1	UNITED STATES FOOD AND DRUG ADMINISTRATION
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3	PEDIATRIC ADVISORY COMMITTEE MEETING
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6	Tuesday, December 7, 2010
7	Bethesda Marriott Hotel
8	5151 Pooks Hill Road
9	Bethesda, Maryland 20814
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11	The meeting was convened at 7:58 a.m.,
12	GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding.
13	MEMBERS PRESENT:
14	GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding
15	AMY CELENTO
16	CARL D'ANGIO, M.D.
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MEMBERS PRESENT: (Continued)
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       HENRY FARRAR, M.D.
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       BRAHM GOLDSTEIN, M.D.
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       JEFFREY KRISCHER, Ph.D.
       KATHLEEN MOTIL, M.D., Ph.D.
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       DANIEL NOTTERMAN, M.D.
 6
       ALEX RAKOWSKY, M.D.
 7
       VICTOR SANTANA, M.D.
 8
      KENNETH TOWBIN, M.D.
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            ALSO PRESENT: WALTER ELLENBERG, Ph.D.,
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        Executive Director and Designated Federal Official
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1	PROCEEDINGS
2	WELCOME AND INTRODUCTORY REMARKS
3	CHAIRMAN ROSENTHAL: I'm going to call to
4	order the committee meeting. If people can start
5	moving to your seats, we'll go ahead and get started.
6	We have a full agenda today, and it's coming on the
7	heels of a great meeting yesterday where we had some
8	wonderful discussions about human breast milk
9	banking.
10	Today's agenda is more typical of what we
11	often do in this committee. We'll be embarking on a
12	number of safety reviews.
13	Let's get started. First just a couple of
14	easy things. If everyone can please silence your
15	cellphones. I'm silencing mine right now. Now I've
16	got a number of witnesses.
17	Then I'd like to start with introductions,
18	if we can please go around the table. Dr. Goldstein,
19	will you get us started again on the introductions.
20	DR. GOLDSTEIN: Good morning. Brahm

Goldstein. I'm Senior Medical Director of Clinical

Research at Ikaria. I'm the industry representative

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- to the PAC, and I'm a pediatric critical care
- 2 physician.
- DR. WOLFE: Sid Wolfe. I'm a general
- 4 internist. I am for today the consumer
- 5 representative on this committee, and with the Health
- 6 Research Group at Public Citizen.
- 7 DR. LA RUSSA: Philip La Russa, Columbia
- 8 University, pediatric infectious diseases. I'm here
- g for the day for vaccine-related work.
- DR. WAGENER: Jeff Wagener, University of
- 11 Colorado. I'm a pediatric pulmonologist and I'm here
- for the day related to the respiratory drugs.
- DR. NOTTERMAN: I'm Dan Notterman. I'm a
- molecular biologist and a pediatric intensivist. I'm
- at Penn State. I'm a member of the Pediatric
- 16 Advisory Committee.
- DR. HOLMES: Greg Holmes, Department of
- Neurology at Dartmouth Medical School, and I'm a
- pediatric neurologist. I'm here for the drugs that
- act on the central nervous system.
- MS. CELENTO: Amy Celento, patient
- representative.

- DR. SANTANA: I'm Victor Santana, pediatric
- hematologist-oncologist.
- DR. RAKOWSKY: My name is Alex Rakowsky.
- I'm a former medical officer at the FDA in the Anti-
- 5 Infective Drug Products. I'm currently the IRB Chair
- at Nationwide Children's Hospital, and after
- yesterday consider myself a donor breast milk banking
- expert.
- DR. MOTIL: My name is Kathleen Motil. I am
- a pediatric gastroenterologist from Baylor College of
- 11 Medicine in Houston and a member of the PAC
- 12 committee.
- 13 CHAIRMAN ROSENTHAL: Geof Rosenthal,
- pediatric cardiologist. For those of you who weren't
- here yesterday, you may hear reference to the meeting
- 16 yesterday. A number of the people who were here
- yesterday may be feeling a little let down.
- 18 (Laughter.)
- 19 I'm sorry. I had a bet at dinner that I
- 20 could work those words into the meeting today.
- DR. ELLENBERG: I'm Walt Ellenberg. I'm the
- 22 Designated Federal Official for the Office of

- 1 Pediatric Therapeutics.
- DR. D'ANGIO: I'm Carl D'Angio. I'm a
- neonatologist. I'm at the University of Rochester.
- I'm a member of the Pediatric Advisory Committee, and
- 5 I'm glad I didn't put any money on that bet at
- 6 dinner.
- 7 DR. SHWAYDER: Tor Shwayder, pediatric
- dermatologist at Henry Ford Hospital in Detroit.
- DR. FARRAR: Hank Farrar, University of
- 10 Arkansas and Arkansas Children's Hospital. I'm a
- pediatrician, clinical pharmacologist, and pediatric
- 12 ER doctor, and I am the patient or pediatric health
- 13 organization representative, representing the
- 14 American Academy of Pediatrics.
- DR. COPE: Judy Cope, pediatrician,
- 16 epidemiologist with the Office of Pediatric
- 17 Therapeutics.
- DR. MURPHY: Dianne Murphy, Director, Office
- of Pediatric Therapeutics, FDA, and pediatric
- 20 infectious disease trained.
- DR. OUSSOVA: Tatiana Oussova, Division of
- Dermatology and Dental Products, FDA.

- DR. KORVICK: Joyce Korvick, Deputy Director
- for Safety, GI Products. I'm here for the debrief
- from the GI Advisory Committee we had last month.
- 4 CHAIRMAN ROSENTHAL: Thank you all very
- 5 much.
- Now, Dr. Ellenberg.
- 7 DR. ELLENBERG: Thank you. Good morning to
- 8 the members of the Pediatric Advisory Committee,
- 9 members of the public, FDA staff. Welcome to the
- 10 meeting. The following announcement addresses the
- issue of conflicts of interest with regard to today's
- discussion of reports by the agency as mandated by
- 13 the Best Pharmaceuticals for Children Act and the
- 14 Pediatric Research Equity Act.
- For Prezista, PegIntron, Xyzal Tablet and
- 16 Solution, Flovent HFA, Acanya Gel, Epiduo Gel,
- 17 Ulesfia Lotion, AXERT, Gardasil, Lamictal, Neulasta,
- and a follow-up on Depakote ER, based on the
- 19 submitted agenda for the meeting and all the
- 20 financial interests reported by the committee
- 21 participants, it has been determined that those
- individuals who will be participating in each topic

- do not have a conflict of interest that presents a potential conflict of interest.
- In general, the committee participants are aware of the need to exclude themselves from the involvement in discussion of topics if their interests would be affected and their exclusion will be noted for the record.
- Wolfe We note that Dr. Sidney is 8 participating as a consumer representative, Ms. 9 Celento is participating as а patient family 10 representative, and Doctors Shwayder, Wagener, 11 Russa, Holmes are participating as temporary voting 12 members. 13
- We would like to note that Dr. Notterman
  will be recused from the discussion of Flovent HFA,
  Lamactil, Lamactil XR, Acanya Gel, Epiduo Gel,
  PegIntron, and AXERT.
- Goldstein is participating Dr. as а 18 nonvoting industry representative, acting on behalf 19 regulated industry. Dr. Henry Farrar 20 participating as a nonvoting industry representative 21 on behalf of the pediatric health organizations. 22

- With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment on.
- Dr. Rosenthal will also provide a brief summary of participation in Cardiovascular and Renal Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee meetings which were held on July 29, 2010, and November 5, 2010, respectively.
- We have an open public hearing this morning

  -- excuse me, this afternoon at 1:00 p.m.
- I just want to remind everybody to turn your microphones on when you speak so that the transcriber can pick up everything that you state, and make sure that you turn them off when you've finished your statement. Again, must make sure that you silence your Blackberries and cellphones.
- 18 Thank you very much.
- CHAIRMAN ROSENTHAL: All right. Dr. Murphy,
  you're going to get us started this morning. I'd
  like to -- for those of you who don't know Dr.
  Murphy, Dianne Murphy is the Director of the Office

- Pediatric Therapeutics in the Office of the 1 Commissioner at the FDA. She's been with the FDA 2. since 1998 and has also served as the Director of the 3 Office of Counterterrorism and Pediatric 4 Development, the Associate Director for Pediatrics, 5 and Director of the Office of Drug Evaluation, with 6 oversight for all of the divisions involved with 7 anti-microbial therapeutics. 8
- She received her medical education from the 9 Medical College of Virginia and completed 10 pediatrics residency at the University of Virginia 11 and a fellowship in pediatric ID at the University of 12 Colorado. She's made many academic contributions and 13 many independent research contributions as 14 She's the editor of a book on office laboratory 15 procedures. 16
- So we're happy to have her as our leader from the Office of Pediatric Therapeutics.

## 19 AGENDA OVERVIEW

DR. MURPHY: We've got to find a way to get
our bios a little shorter, I think. People said they
wanted to know what some of the background was of the

people from FDA since we provide you. So we're working toward the more condensed version.

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Welcome to everybody. I want to express my thanks to everybody being here. This is, as has been stated, more the routine process. We're going to be reviewing the safety profile for products that have studied under either the BPCA, for Children, Pharmaceuticals or the Pediatric Research Act. We have a process which this committee is very familiar with, but we do have a number of new people and I wanted to spend just a moment telling them about our abbreviated process, even though our committee's familiar with it.

Because we go through anywhere from 10 to 15 products at every meeting, the agency tries to provide the committee with its best insights as to what we have been able to find about the adverse events in preparing for this meeting. To assist in moving the -- allowing the committee to focus on the things that are in need of more discussion, we developed a process that is called the abbreviated process.

In that situation, what we will be doing is, Dr. Cope will be getting up and saying with one 2. slide: Here is the product; we've looked at reviews that you're receiving. You will receive, as you requested, the complete review for both the adverse events and the use review. We've looked at that and we do not see any concerning issues that even need a standard presentation. 

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To qualify for an abbreviated review, the usual criteria are that there are no use -- we've had a couple products that actually ended up not being marketed, or there was very little, almost no use in pediatrics -- there are no deaths and very few serious adverse events.

As you will see, there may be a situation where there were deaths, but it's in a population that there is expected that there may be deaths; and actually brought to this committee a request to develop a process for both of the HIV products, where there are a number of deaths that will usually occur when you look at the safety profile for that, and you provided some feedback on that.

So for the new members, we will not be providing a presentation on the abbreviated products.

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It will simply be: Here's the list of products we thought did not have any adverse events, had no safety issues; and do you agree with this, because you've got the background package.

It is an opportunity for you, though, to ask us questions. So that's probably the most important part of what I just said, that if you do have questions, we've brought the division technical experts and scientific experts, asked them to be here, and they will be able to answer any questions. So it's not like we're not inviting you to make It's just we're telling you what assessment is so we can then go on presentations for the standard or expanded products.

We will be having training in this upcoming year. We're going to have even more new members in June. So we will ask you to mark some dates off for training in the coming year. During that -- if you have any thoughts, particularly those of you who have been on the committee, about what would be helpful to

you during that training process, we would like to hear from you about that.

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One of the things that you heard yesterday,
Walt Ellenberg mentioned, was the fact that our
office has taken over the administrative parts of
this committee. In that, we have discovered the
enormous amount of effort that goes into the conflict
of interest review. I bring this up because we are
asking for your patience and understanding, as we did
yesterday, because we haven't been able to hire
people to come and help with all of this.

For one personal loan, we estimate there were over 50 hours put into multiple -- one review was 35 pages written explanation as to why this person should be able to be here.

You are unique -- I was explaining this to one of our new members -- in that you don't come for just one product. So you can understand that the higher you are in an academic institution, the more potential conflicts we have to go through. In this situation, we had to go through over 200 possible imputed conflicts.

So I bring this up because we all believe in transparency and fairness and we want to make sure we do this right and we get the best experts. But we're going to need your patience with us as we go through this. We got that and a lot of help from the individual members who've had to go through this process, this detailed process.

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But we again ask you to please understand that we know that, even though you have nothing to do with the grant, you make no decisions about it, the way the process is is that -- it's called imputed to you. If it's occurring at your institution, it might have the appearance of a conflict. So that's why we have to go through all this justification, and we may have to call you back and get more information.

So again, we really appreciate your patience with us as we go through this.

Now, the last thing is I think good news, but it's going to put another additional responsibility on the committee. You all have noticed over the last couple of years that you've been getting more and more redacted information for

- the medical reviews and you have not been happy about 1 that, because sometimes it has eliminated information 2 you thought you needed.
- So this has occurred because, you know, with 4 the passage of FDAAA we now provide -- the agency 5
- posts not just the summaries, but also the full 6
- medical review for the pediatric studies. 7
- those reviews that go up are redacted, and because of 8
- the volume of materials we've been sending you the 9
- links and copies if you wanted them. But you were 10
- getting redacted material. 11

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- We got clearly the message that that was 12
- causing a problem. So we discussed this and we will 13
- be sending you now unredacted material. Now, you are 14
- a special government employee. We want you to be 15
- informed. But that does provide the additional 16
- 17 two, you have to keep clear in your mind at this

responsibility that you must return that to us; and

- meeting, if you read redacted information, that you 19
- can't discuss it. 20
- So I have a suggestion for you to see if 2.1
- this works. We are going to be sending you a disk. 2.2

- As you know, we always send you a disk with all of 1 the material. We will send the unredacted on the 2 It might be helpful for you in your review to 3 -- if you want to look at the medical review, to look at the redacted one. I'm saying this because if you 5 can read the redacted and you don't have 6 then you don't have to worry questions, about 7 slipping and saying something. 8
- If you need to read the unredacted, you'll 9 know. You hopefully will remember, I needed, I had a 10 question about this and that's what I'm not supposed 11 to talk about. Instead of trying to remember for 12 12 products everything that was a difference between the 13 redacted and the unredacted. I think that will be 14 very difficult for you to remember for all 15 products or 15. 16
  - If anybody has any questions about this when you start next time, we'll have a time to take your questions about any difficulties you have. What you will have to do is bring that disk back. You should not copy it. We will collect it from you.

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For those of you who would like the hard

- copies, we will be sending you the redacted hard
- copies. Again, I think this will be helpful because
- you won't have anything that you could slip and say
- from the hard copy that we're providing.
- Does anybody have any questions about that,
- since you have brought this up a number of times? Do
- you have any questions about that for the next
- 8 meeting?
- 9 (No response.)
- 10 Okay.
- 11 CHAIRMAN ROSENTHAL: I have no question, but
- 12 I do have a comment. I think that this will -- I'm
- appreciative that we are moving in this direction,
- 14 because I think there have been times when the
- discussions at the table have been limited by the
- 16 fact that the information has been limited. So this
- should help us in the deliberations, and I'm
- appreciative of this change.
- DR. MURPHY: And really, as we noted last
- time, we didn't realize how much redaction was going
- on on some of them. They even took the pages out on
- one of them, that obviously made it very difficult

1	for the committee to figure out what was going on for
2	the 100-page medical reviews that now are getting
3	posted.
4	Okay. Dr. Notterman?
5	DR. NOTTERMAN: Thank you, Dr. Murphy.
6	I just wanted to say, as one of the people
7	who had a chance to sample the conflict of interest
8	process, I want to thank your staff and the FDA staff
9	and commend them for their persistence and their
10	skill in working with my staff through adjudicating
11	all of the many potential imputed conflicts so that I
12	could have the pleasure of being at this meeting.
13	DR. MURPHY: As I said, we're new at this,
14	so we really appreciate everybody's patience as we
15	work through doing the administrative parts.
16	We look forward to your discussion, and
17	thank you.
18	BRIEF SUMMARY OF RECENT ADVISORY COMMITTEES:
19	GASTROINTESTINAL DRUG ADVISORY COMMITTEE;
20	CARDIOVASCULAR-RENAL DRUGS ADVISORY COMMITTEE

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CHAIRMAN ROSENTHAL: Thank you, Dr. Murphy.

This is a new process for the next five or

ten minutes. I'll be -- for the new people on the 1 committee, it's not uncommon for members of 2. Pediatric Advisory Committee to be invited 3 participate on other advisory committees at the FDA. That participation is really very important because 5 often the Pediatric Advisory Committee members will 6 have unique perspective and insights that will help 7 the other advisory committees to reach more informed 8 reflections. 9

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But what we're trying that's different is that we are now going to be starting to have the members who've gone off to these other advisory committees come back and report to the Pediatric Advisory Committee just in a brief way what the content was of those meetings. So I'll be reading to you two summary statements, one from the Gastrointestinal Drugs Advisory Committee and one from the Cardiovascular and Renal Drugs Advisory Committee.

Since this is a new process, we always take the opportunity to reflect on our processes, so if this works well or doesn't work well, please give

- feedback, because we can modify this so that it meets
  the committee's needs and wishes.
- 3 Why don't I start with the Gastrointestinal
  4 Drugs Advisory Committee meeting, which was on
  5 November 5, 2010. The meeting was called to discuss
  6 the scientific and clinical basis of the use of
  7 proton pump inhibitors in infants age 1 to 12 months
  8 for treatment of gastroesophageal reflex disease,
  9 including whether and how PPIs should be studied in
  10 infants in the future.
  - There were several members of the Pediatric Advisory Committee that were in attendance, and if any of those people would like to make comments on this summary please feel free to jump in and do so.

- There were several invited experts that came to this as well, and a number of temporary voting members were on the committee. The Pediatric Advisory Committee members who were in attendance were Doctors Rakowsky, Notterman, Santana, and Goldstein, and Dr. Goldstein was a nonvoting member.
- There were also experts in pediatric GI and neonatology serving as temporary voting members, and

- these people included Doctors Richard Martin, Pamela Russell, Colin Rudolph, and Jennifer Lightdale.
- In the past decade -- in the last decade, 3 clinical trials designed to demonstrate efficacy of different proton pump inhibitors in 5 treatment of infant GERD were completed and submitted 6 to FDA for review. The products studied included 7 Meprazol, Lansopryzol, Pantoprazol, 8 Omeprazol, otherwise known as Nexium, Prevacid, 9 Protonics, and Prilosec, respectively. 10
- The FDA determined that these trials failed to establish the efficacy of PPIs for this indication.

The GI Drug Advisory Committee meeting was 14 called to explore the important issues and questions 15 that have been raised about the use of proton pump 16 inhibitors in infant gastroesophageal reflex disease. 17 The agency invite several speakers to discuss a 18 number of things: definitions of gastroesophageal 19 disease and specifically the difference reflux 20 between gastroesophageal reflux and gastroesophageal 2.1 reflux disease, the pathophysiology of GERD in 22

older children, infants, and adults, and 1 differences in the pathophysiology across those ages, 2. survey instruments that were available for assessing 3 GERD, diagnosis and management guidelines for GERD, the safety of proton pump inhibitors -- some points 5 that came up in that realm had to do with the gut 6 biome, necrotizing enterocolitis, and there were some 7 discussion about fractures, which has come up in the 8 Pediatric Advisory Committee as well -- and the 9 clinical pharmacology of proton pump inhibitors, with 10 special emphasis on genetic variability. 11

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So speakers representing the sponsors presented the results of several clinical trials. As I said, these trials failed to demonstrate efficacy of PPIs for treatment of GERD in patients younger than one year.

So the Division of Gastroenterology Products sought advice from and discussion with the advisory committee and the invited members on the following questions: Number one, is the pathophysiology of GERD the same for 1 to 12 month old people versus adults? Two-thirds of the committee voted no to that

- question, but the question was a hard question for the committee to answer in general, because there was -- I would say there was more agreement, there was general agreement, that the definition of GERD in infants is imprecise, for no fault of anyone around the table.
- When asked -- the second question: When 7 acid-suppressing agents are approved for **GERD** 8 indications in adults, should they also be studied in 9 infants? The vast majority of the panel voted yes to 10 this question. 11

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- Third question: Is there a population of infants that should be studied in future trials of acid-suppressing agents? There was a unanimous yes vote, and the populations that were mentioned included infants with cystic fibrosis, neurological impairment, erosive esophagitis, H. pylori disease, esophageal atresia, peptic ulcer disease, and chronic aspiration, and there may have been some others, but these were the ones that I had noted.
- Next question: Are the above responses 22 applicable to neonates and premature infants? The

advisory committee felt yes, but there were 1 special concerns raised for these patients, 2. infants in particular, because premature 3 difficulty in performing some of the diagnostic tests, such as endoscopy, and the greater frequency 5 of apnea as a symptom of gastroesophageal reflux 6

disease in the premature population.

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- The fifth question was: In what indication other than GERD might proton pump inhibitors have a role in infants 1 to 12 months of age? H. pylori disease, peptic ulcer disease, chronic aspiration, and erosive esophagitis were mentioned as possible candidates for other indications.
- There was a very robust discussion. I know that the agency expressed its appreciation to the discussants for a balanced and informative dialogue.
- Are other people who were there -- are other
  people in the room today who were there in a position
  to make any comment? Would anyone like to make any
  comments who was there?
- DR. RAKOWSKY: That was a fair summary. I think you summarized all the discussion at the table.

DR. NOTTERMAN: Geof.

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2 CHAIRMAN ROSENTHAL: Dr. Notterman.

DR. NOTTERMAN: Thanks. I just wanted to make sure one point was emphasized. Several of the consultants mentioned that, notwithstanding absence proof of efficacy for these drugs reflux in infants, nonetheless gastroesophageal they're widely used by the practicing community.

So there is a request that pharmacokinetic and dosage information in this age group be included in the label, for that reason, even in the absence of proof of efficacy.

As a follow-up to that, I DR. SANTANA: thought we had a discussion about -- you reminded me when you made the comment about this issue -- that many of these drugs are being used outside of the GI specialty groups. They're being used by practicing pediatricians, and there really needed to be major educational efforts among those communities present this information so they could make decision about recommending to informed their patients.

1	So I think we were concentrating on the
2	specialty, but we realized that it was much broader
3	than just a specialty and there needed to be efforts
4	to outreach to those groups.
5	CHAIRMAN ROSENTHAL: Yes, thank you. I
6	recall each of those points. Thank you for helping.
7	Question?
8	DR. MOTIL: I was not on that particular
9	committee, but when you commented about the
10	indications for use, I hope that the committee
11	considered an expansion of that group to some
12	specialty areas, specifically intestinal issues
13	related to either short gut or cystic fibrosis.
14	CHAIRMAN ROSENTHAL: I believe those were
15	mentioned, but they're in our transcript, so those
16	comments are accessible.

Other comments on that?

18 (No response.)

19 CHAIRMAN ROSENTHAL: Let me tell you, if you 20 like that one, let me tell you about the -- let me tell you about the Cardiovascular and Renal Drugs 22 Advisory Committee meeting on July 29, 2010.

The Cardiovascular and Renal Drugs Advisory 1 Committee was assembled to discuss the use 2. hemodynamics and specifically pulmonary vascular 3 resistance index to body surface area, or PVRI, as a measure of drug effectiveness in pediatric patients 5 with pulmonary arterial hypertension, as well as to 6 discuss amendment of Pfizer's written request for 7 Sildenafil. I was the only member of 8 the Pediatric Advisory Committee on that panel and 9 the only pediatrician on the panel who was serving as 10 a voting member. 11

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The background is this. The written request for Sildenafil had been amended previously and at this meeting the advisory committee was asked to consider whether FDA should amend the written request again. The existing written request called for the conduct of a single placebo-controlled study with a long-term open label follow-up. The primary end point was exercise capacity.

Pfizer embarked on this trial and it subsequently concluded that the trial was not feasible, primarily because the study could not meet

its enrollment goals due in part to difficulties in determining exercise capacity in pediatric patients.

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Pfizer could have petitioned the FDA to amend the written request to allow them to file for approval with a smaller sample size, but treatment effect was not shown for the primary end point. So Pfizer failed to fulfil the terms of the written request and it had no obvious remedy.

Independent of the issues related to Pfizer's written request, the agency was reviewing its aggregated data from development programs in adults with pulmonary arterial hypertension, looking at possible surrogate markers as candidate efficacy end points. One such marker was PVRI, pulmonary vascular resistance that was indexed to body surface area.

As most of you know, that is a measure that can only be calculated based on hemodynamic data that's obtained at the time of cardiac catheterization. So this surrogate end point was the subject of particular focus, particularly in pediatrics, because so many pediatric patients are

unable to perform the standard exercise testing that can be used in adults.

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So the Cardiovascular and Renal Advisory Committee was asked to examine the case for considering a hemodynamic marker as a surrogate end point for exercise capacity, specifically in the population with pulmonary arterial pediatric The advisory committee was also asked hypertension. whether it believed that Pfizer's written request should be amended again, allowing for a hemodynamic end point rather than the exercise capacity end point that was in the existing written request.

Αt this advisory committee meeting, presentations were made by the agency to review the Best Pharmaceuticals for Children Act and the written request process was reviewed. The particulars if the written process for Sildenafil request presented. A presentation was made by the agency to explore the potential use of change in pulmonary vascular resistance for dosing recommendations children with pulmonary arterial hypertension.

Analyses were performed by the agency which

- demonstrated that changes in PVRI consistently correlated inversely with changes in exercise
- $_{
  m 3}$  tolerance in adults, as measured by the six-minute
- 4 walk distance.
- 5 Pfizer representatives made several
- 6 presentations. These developed the positions that
- 7 pulmonary arterial hypertension is
- 8 pathophysiologically very similar to adult PAH, that
- 9 the study under the existing written request
- realistically could not be completed, that Sildenafil
- is an effective pulmonary vasodilator in adults and
- children with pulmonary arterial hypertension, and
- that a study using PVRI as a primary end point was
- 14 feasible and would be informative.
- So the agency posed a number of questions to
- 16 the Cardiovascular and Renal Drugs Advisory
- 17 Committee. These questions focused on a number of
- things, and I'll run through the topics and then I'll
- 19 talk a little bit about what came up from the
- 20 committee deliberations.
- But the questions focused on the validity of
- 22 pulmonary vascular resistance index as an end point

studies of pediatric pulmonary arterial in 1 hypertension, on similarities and differences in PAH 2. across age groups, on potential trial designs one 3 might consider in the future, on the validity of 4 extrapolation of efficacy from adults to children, 5 and also from older children to younger children, the 6 use of pulmonary vascular resistance indexed to body 7 childhood surface area to study in PAH 8 medications that are already approved in adults for 9 PAH indications. There are no drugs that are 10 approved for pediatric indications for pulmonary 11 arterial hypertension, but there are a number that 12 are approved in adults. 13

And then finally, whether Sildenafil's written request should be amended again to base approval on the evaluation of hemodynamic data, such as PVRI.

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So through the deliberations -- these are my reflections and I'm hoping that they are true to the discussion. One advantage of having a number of people at these meetings is that, as we just heard from the GI advisory committee discussion, it's great

to have other people remember things. We all remember different parts of these conversations. But these are my recollections.

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So the committee members agreed that there is an apparent relationship between PVRI and exercise capacity in adults, but felt that there was not a clear understanding of the extent of this relationship or the conditions under which it holds or fails to hold.

The committee was generally not in favor of using effects on PVRI to extend industry indications other sub-populations of adults because heterogeneity in the pathophysiology and etiology of pulmonary hypertension in adults. Discussants generally took the position that pulmonary arterial hypertension in children has similar symptoms hemodynamics as PAH in adults, but that the etiologies and clinical course may be different.

The committee generally held the position that assessing hemodynamics with cardiac catheterization in the context of study protocols was ethically justifiable and technically feasible. It

was split on the question of whether a treatment effect on pulmonary vascular resistance could be used to demonstrate treatment effect and to derive dosing information for a pediatric PAH indication for products that were already approved for PAH in adults.

The committee suggested several end points that might be suitable for extending a claim to children, including time to clinical worsening, another hemodynamic measure which is the product of the right atrial pressure in the pulmonary vascular resistance, which I think is used in the context of transplant decisions, and the six-minute walk distance.

Suggestions were made about ways to further test the validity of PVRI as an end point, and the notion of a single study to assess the validity of PVRI as an end point was generally supported, with the caveats that PVRI should be assessed at trough drug levels and that the study needed to last for at least 4 to 12 weeks.

Sample size estimates could be based on data

from studies of adults. The committee did not feel 1 there was sufficient -- that sufficient data had been 2. presented to consider the application of PVRI in the 3 pediatric development program for Sildenafil. The FDA was in the process of reviewing additional study 5 data from the sponsor at the time of this meeting, so 6 there was some information that was out there that 7 the committee had not seen, just because of 8 timing of the exchange of information. 9

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As there are currently no reliable reproducible functional end points for the study of drugs to treat pulmonary arterial hypertension in the pediatric population, the potential health impact of these proceedings was great, and the agency again expressed its appreciation for the reflections of the discussants on all sides of the table.

This was quite an interesting meeting from my perspective, and I'll just say on a personal note that it would have -- from my perspective, having more pediatric-minded people around the table might have helped in the discussion. I felt bad because I felt like I couldn't sort of carry the weight of -- I

- couldn't keep up with all the pediatric issues that I
- felt like needed to be addressed, and that if other
- $_{
  m 3}$  people were around the table that maybe some of those
- 4 points would have come out.
- 5 That having been said, I have complete faith
- in the agency to turn over every pediatric rock in
- this process, and I'm sure that it knows that we're
- all her to help. But it was quite an interesting
- g discussion on an important topic.
- 10 Any comments from anyone?
- DR. MURPHY: I just wanted to thank you for
- a very thorough review. These are two very important
- pediatric issues, as you can tell. PPIs are just
- 14 used like water, and this whole issue of an
- alternative end point in a neonatal population with
- serious disease where we don't have another option --
- 17 and this committee meets about I think more
- 18 frequently as individuals and as a committee than
- just about any other committee. So what you're
- hearing us say to you is we want even more.
- 21 We have technical expertise within the
- divisions and on those committees, but we really need

to add pediatric expertise to these committees. So 1 if we call you, we know we're adding to your work 2. burden, but you have a lot of background in what is 3 BPCA, what is PREA. Those people got 4 presentation and they're making recommendations 5

the written request.

- So we really ask that if you can make this 7 an important part of your commitment to helping us to 8 better get these products studied in kids in the best 9 way we can. We really appreciate the time, the 10 thinking, and the effort that goes into this. 11 tell you, we got a long email from Geof after this 12 about his thinking and concerns and wanting to make 13 sure that the pediatric perspective was heard, and I 14 think he did a great job in doing that. 15
- So again, thank you very much, Geof, for that summary.
- CHAIRMAN ROSENTHAL: One of the things about participating on the Pediatric Advisory Committee and working in this capacity with the FDA, I always feel like I get more from the experience than what I bring to it, because the process involves bringing together

so many bright people around the table, and I always consider it a pleasure to participate in this.

The opportunity for having a favorable impact on the public health of children is extraordinary. So I'd just make another pitch. If we're called by the FDA to participate in these discussions, if we can all do it, then really the potential impact is great. So I want to thank everybody for being here today and for participating in each of these advisory committee capacities.

Judith Cope, who wins the distinct honor of having the shortest bio that I've read in two days. Dr. Cope has been with the FDA for the past seven years, working first with the Center of Devices and Radiographical Health on pediatric device-related issues, and then with the Office of Pediatric Therapeutics to focus on pediatric safety for FDA-regulated products.

Her clinical background is in adolescent medicine and general pediatrics, as well as epidemiology. After several years of clinical and

1	academic	practice,	she	received	an	MPH	in
2	epidemiolo	gy and biost	atisti	.cs.			

Her bio is short not because her list of achievements is short, but because she was having mercy on me. So, Dr. Cope, thank you.

## ABBREVIATED PRESENTATIONS:

ACANYA GEL (CLINDAMYCIN/PEROXIDE COMBINATION)

AND ULESFIA LOTION 5 PERCENT (BENZYL ALCOHOL)

DR. COPE: Thanks. Actually, I'm doing the abbreviated presentations, so I wanted to keep my CV short.

But I just wanted to echo what was said,

that FDA really appreciates all the pediatric expert

input at these safety meetings and all the others, as

Dr. Rosenthal summarized.

(Screen.)

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So we're going to just get started right now with the abbreviated presentations for two products.

As Dianne said, we have what we call our abbreviated category. So these two drugs listed before you,

Acanya Gel and Ulesfia Lotion, are both dermatologic products. They underwent full safety reviews, and

- after that the FDA team really assessed there were no serious AEs or deaths that were to be concerning.
- You will note these are used in the 3 population, but there were no safety signals that So we handle this then with the emerged to us. 5 process of no formal presentation. I simply list the 6 two products before you. FDA recommends and feels 7 that we will continue with standard ongoing safety 8 monitoring and that's how we see these two products 9 should be handled. And we would ask you to vote one 10 by one, does the committee concur for this? 11
- We also do ask if -- this is an opportunity

  if you should have any questions on these two

  products. But, Dr. Rosenthal, I'll turn it over to

  you for a vote.
- 16 CHAIRMAN ROSENTHAL: Okay. Just for the 17 record, Dr. Notterman has stepped away from the table 18 because of the perceived conflict of interest, as per 19 the discussion earlier.
- I hope people have had a chance to look
  through all the background material. The FDA would
  like to continue standard safety monitoring for

- Acanya Gel. All in favor -- we're going to do this
- two ways. We'll raise our hands and then go around
- the table and state our votes.
- So for voting, people at the table, if you
- are supportive of continuing standard ongoing safety
- 6 monitoring, please raise your hands.
- 7 (A show of hands.)
- 8 CHAIRMAN ROSENTHAL: If you are opposed?
- 9 (No response.)
- 10 CHAIRMAN ROSENTHAL: Let's go around the
- table. Dr. Wolfe, can you get us started?
- DR. WOLFE: I support the recommendation.
- Is there anything else that I am supposed to say?
- 14 CHAIRMAN ROSENTHAL: That's fine.
- DR. LA RUSSA: Philip La Russa, concur.
- DR. WAGENER: Jeff Wagener, agree.
- DR. HOLMES: Greg Holmes, agree.
- DR. KRISCHER: Jeff Krischer, agree.
- MS. CELENTO: Amy Celento, agree.
- DR. SANTANA: Victor Santana, agree.
- DR. RAKOWSKY: Alex Rakowsky, agree.
- DR. MOTIL: Kathleen Motil, concur.

- DR. D'ANGIO: Carl D'Angio, agree.
- DR. SHWAYDER: Tor Shwayder, agree. And as
- the only dermatologist, I'll add a comment. I was
- actually shocked at how long a percentage the Acanya
- 5 Gel had a favorable response rate, since I use
- ferential retinoids and benzyl peroxides probably 30 times a
- day.
- The second comment is the Ulesfia Lotion,
- 9 which is a very good product, but the efficacy rating
- 10 was sullied by the fact that so few of the centers
- actually looked at the other children in the home.
- So you could cure the one kid, they go home and get
- it back from their brother. That was a huge gap in
- the setup of the project. Other than that, I think
- they're both fine products and I concur.
- DR. TOWBIN: Good morning. Kenneth Towbin.
- 17 Yes.
- 18 CHAIRMAN ROSENTHAL: All right. Would you
- like to move on?
- 20 Are you next?
- DR. COPE: So those were votes for both of
- 22 them?

- 1 CHAIRMAN ROSENTHAL: Oh. You know what, we
- 2 kind of discussed -- okay. I was expecting two
- 3 slides.
- DR. COPE: Sorry. I kind of packaged it.
- CHAIRMAN ROSENTHAL: No, thank you. Thank
- 6 you. That's in the spirit of abbreviated reviews.
- 7 So let's vote on -- I'm sorry. Everyone
- around the table, the vote that I intended to happen
- yas for Acanya Gel. Is that what we all voted on?
- 10 So let's vote again on the second product,
- on Ulesfia Lotion. All in favor of continuing the
- 12 standard ongoing monitoring?
- (A show of hands.)
- 14 CHAIRMAN ROSENTHAL: Anyone opposed?
- 15 (No response.)
- 16 CHAIRMAN ROSENTHAL: Again, it appears to be
- unanimous. Dr. Wolfe?
- DR. WOLFE: I agree with my first comment.
- DR. LA RUSSA: Same.
- DR. WAGENER: Jeff Wagener, agree.
- DR. HOLMES: Greg Holmes, agree.
- DR. KRISCHER: Jeff Krischer, agree.

- MS. CELENTO: Amy Celento, agree.
- DR. SANTANA: Victor Santana, agree.
- DR. RAKOWSKY: Alex Rakowsky, agree.
- DR. MOTIL: Kathleen Motil, concur.
- DR. D'ANGIO: Carl D'Angio, concur.
- DR. SHWAYDER: Tor Shwayder, concur.
- 7 DR. TOWBIN: Kenneth Towbin. Yes.
- 8 CHAIRMAN ROSENTHAL: Dr. Notterman, I'm
- g sorry to do this to you. For the second product, for
- 10 Ulesfia Lotion, you do get to participate in the
- voting. So I'm wondering what your vote would be
- regarding whether FDA should continue ongoing safety
- monitoring for this product?
- DR. NOTTERMAN: Well, were I to participate
- 15 I would concur with continued monitoring.
- 16 CHAIRMAN ROSENTHAL: Thank you. Now, if you
- don't mind stepping away from the table for the next
- 18 discussion.
- DR. COPE: Thank you very much.
- 20 CHAIRMAN ROSENTHAL: Dr. Notterman, I really
- appreciate your sense of humor in all this and your
- help.

1	Our next speaker is Dr. Durmowicz, and I'r
2	looking for a bio for you. Oh, here it is. Dr
3	Durmowicz joined the Pediatric and Maternal Healt
4	Staff in March of 2008. She received her medica
5	degree from the University of Cincinnati College of
6	Medicine and she completed her internship and

- 7 residency in pediatrics at University of Colorado
- 8 Health Sciences Center.
- pr. Durmowicz's area of clinical interest is
  in the care of children and youth with special health
  care needs. She's practiced in both academic and
  community care settings.
- Dr. Durmowicz is a familiar face because she's helped us on a number of these products. So thanks for joining us again.
- DR. MURPHY: Dr. Rosenthal, we'll have representatives of the divisions come to the table, so can I have them introduce themselves?
- 19 CHAIRMAN ROSENTHAL: Thank you.
- DR. LIEDKA: Jane Liedka, medical officer with the Division of Dermatology and Dental Products.
- 22 (Screen.)

1 EPIDUO GEL (ADAPALENE AND BENZOYL PEROXIDE)

DR. DURMOWICZ: Thank you, Dr. Rosenthal,

and good morning. I am pleased to present the

pediatric focused safety review for Epiduo.

5 (Screen.)

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6 My presentation will follow the outline, 7 which is similar to those presentation that have been

presented at different advisory committees.

(Screen.)

Epiduo is a combination product containing 10 adapalene, a retinoid, and benzoyl peroxide. The 11 product was approved in December of 2008 for 12 daily topical treatment of acne in patients 12 years 13 of age and older. The product has an outstanding 14 study requirement under PREA to evaluate the safety 15 and efficacy of Epiduo in patients 9 to 11 years with 16 acne vulgaris. 17

18 (Screen.)

Epiduo was evaluated in two 12-week, multicenter, randomized, controlled safety and efficacy studies in patients 12 years of age and older with acne. The superiority of the combination product was

demonstrated over each of the components and over placebo, and no unexpected adverse events were

3 identified.

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(Screen.)

This slide provides the safety information 5 included in the labeling. The warnings 6 precautions warn of risks associated with exposure to 7 UV light and weather extremes and of local cutaneous 8 reactions, specifically erythema, scaling, dryness, 9 and stinging-burning. 10

The adverse reactions section of labeling informs of events identified in clinical studies that occurred in at least one percent of patients. These were all local reactions. In addition, a table with the incidence of cutaneous irritation is provided. This safety information is also provided in the patient counseling information section.

(Screen.)

This slide provides information about the use of Epiduo in the outpatient study for the 19-month period after product approval. Approximately 930,000 Epiduo prescriptions were dispensed to almost

- 1 600,000 unique patients. Pediatric patients 0 to 11
- years accounted for approximately 20,000 of these
- 3 prescriptions and for approximately 15,000 unique
- 4 patients.
- 5 (Screen.)
- Moving to the adverse events since marketing
- approval the AERS database was searched for reports
- associated with Epiduo. A total of seven reports
- were identified. Three of those were in patients 0
- to 16 years and all three of the pediatric reports
- 11 were considered serious.
- 12 (Screen.)
- Looking more closely at the pediatric
- adverse reactions, two of these were considered local
- skin irritation reactions. The first was in a 15-
- 16 year-old boy with irritation, itching, and facial
- erythema after two days use of an adapalene benzoyl
- 18 peroxide product. The events resolved after product
- 19 discontinuation, but non-severe irritation was
- reported with restart of the medication.
- The second report was of a 16-year-old
- female with erythema, papules, yellow erosive

1 reaction, weeping and swelling after use of Epiduo

for 14 days. Epiduo was discontinued. The patient

was treated with a topical antibiotic and the patient

was reported to improve.

5 (Screen.)

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The third report is a 16 year old who reported facial swelling and throat closing after seven days of Epiduo use. Epiduo was discontinued and the patient was treated with an unknown antihistamine and ice, with resolution of the symptoms. Epiduo was later restarted and the events

Of note, all three patients have also reported use of topical skin care products. Of note, the Epiduo labeling for local skin reactions includes erythema, contact dermatitis and irritation, but not hypersensitivity.

18 (Screen.)

recurred.

Looking at the adult adverse event reports,
there were three reports of severe cutaneous
reaction; a 20 year old with an extensive acute
bullous and vesicular eczema and eyelid edema after

- one-time use of Epiduo; a 24 year old who used Epiduo sporadically reports eyelid edema and pruritus within hours of application of the product. The events resolved with discontinuation, but eyelid edema, systemic pruritus and a chest rash were reported on restart of the medication.
- An 18 year old with acute eczema of allergic 7 type with edema, weeping and skin induration after 8 one-time use of Epiduo was the third adult case. 9 Although the Epiduo was stopped, the symptoms 10 persisted and the patient reported to be unable to 11 The patient was treated with speak or swallow. 12 prednisolone and topical therapy with resolution. 13 Subsequent patch testing did reveal strong positive 14 reaction with Epiduo and benzoyl peroxide. 15
- The fourth and final report was of worsening acne.
- 18 (Screen.)
- An additional serious report was received in the AERS database after the pediatric focused safety review was completed in June. This report is of a 16 year old female who reported facial swelling after

three days of Epiduo use. Despite treatment with 1 oral steroid, swelling continued and the patient 2 throat swelling. Intramuscular reported 3 dexamethasone was administered. This was a foreign 4 report and both medications were administered by the 5 mother, who is reported to be a pharmacist. 6

(Screen.)

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Given the findings and the AERS review, a 8 literature review was performed to identify case 9 reports of adverse events, specifically serious 10 cutaneous reactions, including severe local edema and 11 possible anaphylaxis, for adapalene and benzoyl 12 Three articles were identified, peroxide. 13 reporting a delayed hypersensitivity reaction in one 14 adult patient. All articles reported a positive 15 dechallenge and positive rechallenge, and 16 articles reported positive patch test results to 17 benzoyl peroxide. 18

19 (Screen.)

In summary, our safety review identified the concern of an association of hypersensitivity with Epiduo use. Current labeling was approved at the

- time of product approval and does not contain
- 2 postmarketing experience information. The division
- 3 is reviewing the patient findings and current
- 4 labeling.
- 5 (Screen.)
- The FDA will continue its standard ongoing
- 7 safety monitoring. We're wondering if you concur
- 8 with that suggestion?
- g (Screen.)
- 10 I'd like to thank the following individuals
- for their help with the presentation.
- 12 CHAIRMAN ROSENTHAL: Thank you.
- Are there questions? Yes, Dr. Rakowsky.
- DR. RAKOWSKY: Thank you, Dr. Durmowicz, for
- your presentation. In regard to that slide before
- where you say the division is reviewing the safety of
- findings and current labeling, so does that mean that
- they're considering adding the hypersensitivity or is
- that a topic that's still going to be looked at in
- the future more closely? I'm not sure exactly what
- is meant by "identified the concern" and then
- reviewing.

DR. OUSSOVA: We are considering it and we 1 are at the stage of discussing it with the sponsor 2. and the label will be updated.

- DR. RAKOWSKY: So essentially what we're voting for is that this has been identified, not so 5 much voting to put it in the label, but to discuss it 6 further with the sponsor, is what we're being asked 7 to concur with, right? 8
- DR. MURPHY: You guys can comment. 9 Sometimes we do come and say, this is what we've 10 identified, we want to put it in the label. 11 didn't say quite that this time because they're in 12 the midst of negotiations. But you can say what you 13 think. 14
- So if you don't -- in other words, anywhere 15 from, gee, it was only one or two cases, to, we don't 16 know that you need to do this, to, gee, these were 17 life-threatening. You're here to comment on what you 18 think the safety signal is. 19
- CHAIRMAN ROSENTHAL: Yes, Dr. Santana. 20
- DR. SANTANA: So is this benzoyl peroxide 2.1 hypersensitivity issue a class effect across all 22

- 1 products that have benzoyl peroxide, and therefore
- $_{\rm 2}$   $\,$  when it's identified in one it carries over to the
- 3 others, in terms of labeling?
- DR. OUSSOVA: No. We deal with each
- 5 individual product and we update the label based on
- the individual product's adverse events reporting.
- 7 DR. SANTANA: What about products that have
- 8 benzoyl peroxide? Has this signal also been
- j identified, either in adults or kids?
- DR. OUSSOVA: Well, for example, Acanya --
- 11 CHAIRMAN ROSENTHAL: Please use your mike.
- DR. OUSSOVA: Acanya Gel also has benzoyl
- peroxide as a component and, as you heard, we did not
- 14 identify similar adverse events in that product. So
- no, we do not use the class labeling.
- DR. SHWAYDER: I have I guess a couple
- questions. My gestalt on all these is that they're
- the benzoyl peroxide irritant rather than allergic
- phenomenon, with the exception of the one where they
- had the throat swelling, which I can't explain.
- Benzoyl peroxide is ubiquitous. Most of the
- over-the-counter acne medicines from ProActive to the

- stuff you buy in the hallways of the airports on the
- way to your date have benzoyl peroxides in them. My
- own son had an immediate erythema reaction to benzoyl
- peroxide the first time he used it.
- Did you see the signal with adapalene? I
- 6 didn't see it in there. Adapalene's fairly new.
- 7 It's been out less than five years, I think.
- DR. LIEDKA: Adapalene has been --
- GHAIRMAN ROSENTHAL: You just turned off
- 10 your mike.
- DR. LIEDKA: Sorry. Adapalene has been
- reported to cause both irritant and allergic contact
- dermatitis, as has benzoyl peroxide. They can cause
- 14 both types of reaction.
- DR. SHWAYDER: I guess that answers my
- 16 question.
- I think there's millions, if not billions,
- of people who have used benzoyl peroxide, just
- because of the ubiquity of the thing. I have nothing
- 20 more to say other than I encourage you to continue
- following, without anything more severe.
- 22 CHAIRMAN ROSENTHAL: Any further discussion

- on the swelling in the throat issue? Dr. D'Angio.
- DR. D'ANGIO: I had a question that I think
- just reflects my ignorance, despite having done this
- 4 many times. In the safety review there are
- recommendations. Am I correct in assuming that's the
- sort of thing -- that that's what's being discussed
- y with the sponsor, the recommendations for label
- 8 changes?
- DR. OUSSOVA: Yes, that's what they're
- discussing with the sponsor.
- 11 CHAIRMAN ROSENTHAL: Any further comments,
- 12 discussion?
- (No response.)
- So does the advisory committee concur with
- the approach that has been discussed? And I guess
- that approach is just continuing to speak with the
- sponsor about label changes.
- DR. WAGENER: Just a question.
- 19 CHAIRMAN ROSENTHAL: Yes?
- DR. WAGENER: Can you divulge what the
- discussion with the sponsor about label changes are?
- Because what we saw here was the perception that you

- were going to continue to monitor, and yet you're also requesting label changes, or you're talking with
- 3 them about it.

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- DR. OUSSOVA: Basically, the discussion is about labeling changes and continuous monitoring, for us to continue monitoring. What we are discussing, I cannot give you the details because that discussion is not final. But the discussion is to update the label with the events of hypersensitivity.
- DR. MURPHY: If the committee -- you know,
  we get into this frequently, where we've discovered
  something during the review. We sometimes have time
  to go back and get additional information and get to
  the company and come up with a definitive sort of,
  this is what we want to put in the label.
  - In this situation, you have the safety review recommendations for what they want, what the safety group said. The division is now in discussions and, because they are, they don't have anything definitive to say to you.
- You can say, we think you should have something about the severe reaction, or you can say,

- we leave it up to you. That's what we're trying to
- 2 say. If you think that you want to make additional
- g comment to the division, that's fine, because there
- are -- that's why you get the review, so you can have
- the individual cases and you can make suggestions.
- As you well know, the majority of the time
- the division takes it, but they don't always. But
- g that -- again, it doesn't have to be just the
- 9 process, Geof. As somebody pointed out, there are
- 10 recommendations here. If you like those
- recommendations, you think that's -- if you agree
- with those, that would be fine. If you don't agree
- with those or you just want to leave it up to the
- division -- again, the spectrum is on the table for
- 15 you.
- 16 CHAIRMAN ROSENTHAL: Dr. Shwayder.
- DR. SHWAYDER: Can you go back to the slide
- that had the throat swelling? Was that the one that
- 19 was foreign?
- 20 (Screen.)
- DR. DURMOWICZ: The pediatric case, that was
- actually a domestic case.

- DR. SHWAYDER: Did they have any other
- variables? Was the kid eating a peanut butter and
- jelly sandwich at the time?
- DR. DURMOWICZ: I don't recall any other
- details that would really shed any additional light.
- DR. SHWAYDER: It's really, really hard to
- deal with the N equals one.
- DR. LIEDKA: There was some follow-up on
- 9 that case. The reviewer spoke with the reporter on
- the telephone. Apparently the patient did retry the
- 11 Epiduo a few days later and did have a recurrence of
- her symptoms, but there was no hospitalization, there
- 13 was no sequelae from that.
- 14 CHAIRMAN ROSENTHAL: Were you going to say
- something? Please just let us know who you are.
- DR. SALAAM: Tracy Salaam, Office of
- 17 Surveillance and Epidemiology, Division of
- 18 Pharmacovigilance I.
- I was just going to reiterate what Dr.
- Liedka said, that there was some follow-up with the
- 21 reporter. The reporter was the mother and she did
- say, again, that they did retry the medication. They

- weren't really sure exactly what happened with the
- 2 child. They weren't sure that the product was
- actually what was causing the reaction. So she did
- give her daughter the medication again, and her
- 5 daughter did have the same reaction. It did clear
- 6 within a few days.
- 7 CHAIRMAN ROSENTHAL: Dr. Wagener, did you
- have a comment?
- DR. WAGENER: Yes. I'd just like to follow
- up I think what Dr. Santana said earlier as far as
- the class effect question. I don't think there's any
- question but this girl had an IGE-mediated reaction,
- but that's a published response to this, to benzoyl
- 14 peroxide.
- So the question I guess would be whether or
- not as a class of drugs, given published experience
- in adults and given this case in kids, you want to
- 18 put hypersensitivity in. Needless to say, that
- includes all benzoyl peroxide drugs, which we've
- heard is quite an extensive class.
- But I wouldn't debate that this was --
- 22 whether it was IGE or a local response. It's a

- systemic response. 1
- CHAIRMAN ROSENTHAL: Yes, Dr. McMahon. 2
- Ann McMahon, Division DR. McMAHON: 3 Pharmacovigilance I, Office of Surveillance 4
- Epidemiology. 5

the table.

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- I just wanted to mention that the post-6 reports, this one was а marketing positive 7 rechallenge report. There's a lack of -- even though 8 this is a relatively compelling report in some ways, 9 there are a lot of details, as alluded to earlier, 10 that may or may not be available. Also, this is a 11 combination product. I just wanted to put that on 12
- CHAIRMAN ROSENTHAL: Dr. Wolfe.
- DR. WOLFE: I think what it sounds like is 15 troubling some people is the wording, which 16 "reflect that Epiduo Gel should not be administered 17 to individuals who are hypersensitive to adapalene, 18 benzoyl peroxide, or any of the components." So if 19 that recommendation is taken seriously, then by 20 implication you would need to put it in because it's 21 an "or", not "and." So there are people we know 22

- about with hypersensitivity to benzoyl peroxide.
- So I think either the recommendation maybe
- needs to be reworded or we are de facto voting that
- any product that has benzoyl peroxide would need to
- have that warning. That's what the dilemma sounds
- 6 like to me.
- 7 CHAIRMAN ROSENTHAL: Nicely summarized.
- 8 Let's go back. Other points of discussion
- on this product, or are there other things that the
- 10 committee should be thinking about regarding this
- product before we move on?
- (No response.)
- 13 Have you heard enough?
- DR. MATHIS: I'm sorry. I just want to
- reiterate that the charge of this committee under the
- law is to look at the adverse events that have been
- 17 reported and make any recommendations for labeling.
- 18 I don't think that the charge is to make
- 19 recommendations based on an assumption that the
- 20 company has agreed to certain labeling. So at this
- 21 point I think your recommendations and vote should
- reflect the current situation and the current

- 1 labeling.
- CHAIRMAN ROSENTHAL: So the question before
  us is whether we concur with your approach. But I
  guess what we're saying is that maybe we should
  change the question and ask -- and just ask the
  committee whether the committee feels that the label
  should more strongly reflect this hypersensitivity
  issue.
- DR. MURPHY: I think that's a good summary. 9 The committee can change the question if you don't 10 think it gets to what you want to say. In other 11 words, if you want to say more than "we agree with 12 negotiating with the company," and you want to say 13 "we specifically want, would recommend that you have 14 something about this reaction in the label for this 15 product, or this reaction for the class, " you can do 16 that. 17
- 18 CHAIRMAN ROSENTHAL: Yes, Dr. Santana.
- DR. SANTANA: As somebody alluded to earlier, an N of one is always very difficult to make a decision on. I guess -- so I have no problem with an N of one and making a judgment call on an N of

- one. But I guess what I still haven't heard is,
  having identified this as a potential safety signal,
  is the agency going to look at this class of
  compounds in toto and come back to us at some future
  point and say, we have reviewed this class of
  products and we don't feel it's a class issue, it may
  be related to X or Y drug, but it's not a class
  issue?
- for, not necessarily that we're going to do something different, but that we have identified, or you have identified, a signal and we would like you to go back and give us more information from the class issue. That's all I was trying to allude to when I asked the class effect issue.
- I know you don't have the data right now. I know that. So you're asking us to answer a question, and I feel comfortable answering the question with an N of one today, but I want a reassurance that you're going to go back and look at this class issue if it does exist and reassure to us that it is not a class issue. That was my point.

1 CHAIRMAN ROSENTHAL: Dr. Wolfe.

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DR. WOLFE: Just a further brief comment, 2 which is it is possible, although the data that's 3 been presented in the material we got doesn't really support that, that there is some synergistic effect 5 between the retinoid receptor adapalene and benzoyl 6 peroxide, in which case you wouldn't have to impute 7 that the whole class of benzoyl peroxide-containing 8 products is dangerous. 9

I think we would strongly encourage the FDA to pursue that possibility. The rechallenge is with the combination product, not with individual ingredients. So I think that the approach that you mentioned, Geof, is a good one. We want them to keep going on and explore particularly the issue, as you just said, of whether or not there's some evidence that this is a unique property of this combination or whether it really is benzoyl peroxide.

I would be a little bit surprised if it was just benzoyl peroxide because we have had, as mentioned by a number of people, an enormous amount of experience with this. So it may be, hypothesis,

something about this combination. Please explore it.

CHAIRMAN ROSENTHAL: Would people be willing 2 to vote on the question if I reframed it and said --3 and asked the question, does the advisory committee 4 concur with the approach to Epiduo as long as it 5 considers inclusion of -- as long as it includes a 6 discussion with sponsor around the 7 of hypersensitivity issue? That sort draws 8 particular focus to the one issue that we've been 9 discussing at the table and allows the agency to know 10 that this is an issue that we feel strongly enough 11 about that we feel it really requires some further 12 attention. 13

Is that okay?

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That would be very helpful. DR. MURPHY: 15 Fundamentally, we've done what we could do. 16 looked at the literature. You saw two other products 17 that have benzoyl alcohol and we didn't see this. 18 But you're telling us you want us to consider is this 19 this class effect or is it combination 20 particularly, and that we need to look at that, 2.1 because this appears to be, even though it's an N of 22

- one, a fairly documented, if you will, rechallenge case of hypersensitivity reaction, of severe hypersensitivity reaction.
- Just so I make sure I understand, 4 you're saying is that if it turns out that it's not a 5 class effect, that the case stands and we can't -- we 6 have only these few cases, do you want us to continue 7 to wait for more cases or do you think we should put 8 something in the label? That's really what it's 9 coming down to, is do we move forward with the 10 If we get more information information we have now? 11 that helps us decide that definitely there are more 12 cases out there -- right now it doesn't look like it 13 -- then it's easier. 14
  - But if we don't have any additional cases, then at this point are you comfortable with us continuing to look for cases of this hypersensitivity severe reaction with this combination product, or do you think we should put something in the label in the interim? I think that's sort of where we are at this point.
- 22 CHAIRMAN ROSENTHAL: Dr. La Russa, Dr.

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- 1 Wagener, and Dr. Towbin, in that order.
- DR. LA RUSSA: Now I'm a little confused.
- 3 Have you done as much as you possibly can at this
- 4 point to look for a class effect, or can you go back
- and look at more data that you already have, or do
- you have to continue to look prospectively?
- 7 DR. SALAAM: Tracy Salaam. We've looked at
- benzoyl peroxide just in the literature and we've
- 9 looked at adapalene by itself in the literature as
- 10 well. We did not find any reports for adapalene.
- 11 The three reports that we found in the literature for
- benzoyl peroxide were in Dr. Durmowicz's slides.
- 13 CHAIRMAN ROSENTHAL: Dr. Wagener.
- DR. WAGENER: I might be a little more
- assertive, but I also might get kicked off the
- 16 committee, so I have to be careful here.
- 17 CHAIRMAN ROSENTHAL: I doubt that. We're
- interested in your opinions, even when they're strong
- ones, and perhaps particularly when they're strong
- 20 ones.
- DR. WAGENER: Well, as Dr. Durmowicz will
- testify, I'm a great one for the anecdote's power.

So an N of one I would say is pretty powerful. So 1 what I might suggest is that we recommend that 2. hypersensitivity be added to this product based on N 3 of one plus the literature review which shows that it 4 can occur, so they're consistent. And too is that we 5 follow that recommendation with encouraging 6 agency to follow through with their plans, existing 7 plans, to better look at the class or to look at 8 whether or not there's a specific interaction between 9 amplify these two drugs that that may 10 hypersensitivity possibility, and leave it at that. 11

12 CHAIRMAN ROSENTHAL: Thank you.

Dr. Towbin.

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If I heard correctly, one of DR. TOWBIN: the things that we're being asked to do is also make some statement about the recommendations that came from the safety review. In looking at the wording of that and the data that's been presented, it's a little bit apples and oranges, because the contraindications are for people with known hypersensitivity reactions already.

So it seems to me that one of the things

we're being asked about is to consider the safety 1 features of a population of patients who've already 2 had a hypersensitivity reaction to benzoyl peroxide 3 products. I just want to get a sense from the group, how comfortable would you be giving this to somebody 5 who would come in with a previous well-documented 6 hypersensitivity reaction, and whether 7 contraindication isn't in some ways a pretty logical 8 extension, that if someone has had a known and 9 confirmed case would you want to have people be aware 10 of that risk? 11

12 CHAIRMAN ROSENTHAL: Yes?

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DR. SHWAYDER: Just a couple comments. I don't know if it's like a tempest in a teapot adding hypersensitivity to it, because it seems it's very logical. If you're allergic to it, don't use it. So I have no problems with that at all. I don't know if it changes their marketing or everyone on Wall Street is going crazy at the moment.

The second thing is, retinoids and benzoyl peroxide have been used, the two tubes at the same time, since retinoids came out in the early 1980s.

- This is just sort of a me-too, putting it together so
- it saves a step. But since 1980 I've been writing
- for them separately and I tell them to put it on. So
- if there had been a signal, I would have expected the
- 5 signal at this point.
- 6 CHAIRMAN ROSENTHAL: Yes, Dr. Farrar.
- 7 DR. FARRAR: This is -- hypersensitivity
- reactions happen all the time. This is not -- we're
- not talking about -- yes, they're rare, but compared
- to a lot of stuff. I think what they've got in their
- recommendations is pretty reasonable. If you've had
- a hypersensitivity reaction to something like this,
- don't use it, and warn people.
- I get a lot of calls where they go, I've
- smeared this stuff on somebody and their eyes swelled
- up, or something like that; could that have happened?
- 17 Could that be due to the drug? The answer is always
- yes. So there's nothing -- I think they're handling
- this appropriately to try to get the company to put
- these comments in there, just so that they're in the
- literature for people to look at.
- But I'm not sure that we need to chase it

- much further than that, because this stuff -- I would
  be surprised if there's any drug out there that has
  not had a hypersensitivity reaction of some sort to
- it at some time or another.
- So is it fair for me to CHAIRMAN ROSENTHAL: 5 frame this as that the committee's recommendation 6 will be to continue discussions with the sponsor 7 about including wording around hypersensitivity, and 8 then also to consider looking for class effects 9 related to benzoyl peroxide, and circle back to the 10 committee in some abbreviated way at some point in 11 the not-too-distant future? Does that sound good? 12

Dr. Wolfe.

DR. WOLFE: Is there any labeling right now on benzoyl peroxide that says if you previously have evidence of sensitivity that you shouldn't use it?

Because if that's the case already, then it makes it even more obvious that we should go with this kind of recommendation.

No one is saying don't use benzoyl peroxide.

That would be off the wall. And since there are

literature cases of people allergic to it, companies

- tend, for various reasons, to cover their legal bets,
- and if it is known that even a substantial number of
- 3 people have a hypersensitivity to something like
- benzoyl peroxide they would say, if you have previous
- 5 hypersensitivity don't use it.
- Is that the case right now for benzoyl
- 7 peroxide labeling?
- DR. MURPHY: Well, we're trying to look at
- q the labels of the other two right now to see. Right
- now, this product's contraindications does not have
- that. The present label, you have it in your disks
- or your binder. At least the label we're looking at
- right now, if you go to -- can you go to --
- 14 CHAIRMAN ROSENTHAL: It's in the background
- materials that we've each received.
- DR. COPE: Yes. It's the last section.
- DR. MURPHY: Yes.
- DR. OUSSOVA: Your question is whether this
- is in the contraindications on the current label?
- DR. WOLFE: Just for the benzoyl peroxide,
- 21 yes.
- DR. MURPHY: We know it's not for this

product, and we're looking to see for the others.

2 (Pause.)

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DR. MURPHY: Here's what Acanya says under 3 contraindications. Ιt says: "Acanya is patients contraindicated in with a history 5 regional enteritis, ulcerative colitis, or" -- that's 6 what's in contraindications for that one. 7

But as far as the benzoyl, we don't have anything in there for that.

DR. OUSSOVA: I just wanted to make a general comment, since we have lots of labels that are in kind of an old format, and in those labels the contraindication section does have this kind information. But we are now moving to a different, more comprehensive format of the labeling and in most labels, since most drugs, as someone mentioned patients can experience already, hypersensitivity, and by the Code of Federal Regulations we do not put this kind of information in the contraindications subsection of the label because this is something that is difficult to prevent from occurring and the physicians know the patient has

- already experienced this hypersensitivity with the
- 2 particular product. And it's a common practice not
- 3 to recommend this product to these patients any more.
- DR. WOLFE: It's a common practice, but it
- isn't in the label. Or at least it's not in the
- 6 contraindication.
- 7 DR. OUSSOVA: It's not in the
- 8 contraindications section in the newest labels.
- DR. WOLFE: Is it anywhere in these older
- 10 labels?
- DR. OUSSOVA: It's somewhere on the label
- 12 and it says, and probably in warnings and
- 13 precautions, that if patients develop adverse
- 14 reaction discontinue the use.
- 15 CHAIRMAN ROSENTHAL: So would people feel
- 16 comfortable having that type of wording in the label
- for Epiduo, that if patients were to experience
- 18 hypersensitivity then discontinue its use, rather
- than put it in the contraindication area? Dr.
- 20 Rakowsky?
- DR. RAKOWSKY: Can I instead propose what
- you proposed initially, that what we're going to vote

- for is that the division is looking into this, it has
- an N of one, and let them go through the due process
- of then deciding and come back to us. Your
- wording from your last, a few minutes ago.
- CHAIRMAN ROSENTHAL: Dr. D'Angio, are you
- going to suggest that we vote on this?
- 7 DR. D'ANGIO: I can close my comments with
- 8 that, yes. It sounds as if there is disagreement
- g down that end of the table about where this -- what
- should be done with these data. There are people
- 11 within the safety reviewers wanting to put it in
- contraindications. We have the dermatology people
- saying that that's not where it belongs.
- I think that the wording that Geof suggested
- is fine and we should vote.
- DR. MURPHY: Remember, that's what we're
- supposed to let you know. In other words, we don't
- have to all agree. That's one of the points, is that
- we're going to bring you the recommendations from one
- 20 group and another group may not have the same
- opinion. But that's why you're here. So we want
- your input.

CHAIRMAN ROSENTHAL: So here's the question. 1 We won't be discussing this any more. The question 2. Does the advisory committee concur with the is: 3 agency's approach to Epiduo, as long as it includes 4 discussion of label changes to address the issue of 5 hypersensitivity? All in favor? 6 (A show of hands.) 7 CHAIRMAN ROSENTHAL: Any opposed? 8 (No response.) 9 CHAIRMAN ROSENTHAL: Please, Dr. Wolfe, 10 sorry. Will you get us started again? 11 DR. WOLFE: We've reached a very pleasant 12 compromise here. 13 DR. LA RUSSA: Philip La Russa, concur. 14 DR. WAGENER: Jeff Wagener, agree. 15 DR. HOLMES: Greg Holmes, agree. 16 DR. KRISCHER: Jeff Krischer, agree. 17 MS. CELENTO: Amy Celento, agree. 18 DR. SANTANA: Victor Santana, agree. 19 DR. RAKOWSKY: Alex Rakowsky, agree.

DR. MOTIL: Kathleen Motil, concur.

DR. D'ANGIO: Carl D'Angio, agree.

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- DR. SHWAYDER: Tor Shwayder, agree.
- DR. TOWBIN: Kenneth Towbin, agree, with the
- additional comment that I appreciate the language
- that is recommended by the safety review, lest
- 5 someone think that there would be something safer
- about this product than others that contain benzoyl
- 7 peroxide.
- 8 CHAIRMAN ROSENTHAL: All right. We're
- a little behind schedule, but this is exactly the
- kind of discussion that the agency appreciates.
- So let's move on now to our discussion of
- post-marketing monitoring of vaccine safety. We're
- moving into the Gardasil discussions. I'd like to
- 14 introduce Dr. Rickey Wilson, who's the Deputy
- Director of the Division of Epidemiology in CBER's
- 16 Office of Biostatistics and Epidemiology. This
- 17 division is responsible for post-marketing safety
- surveillance of CBER-regulated products.
- Dr. Wilson received his medical degree from
- the University of Texas Health Science Center in San
- 21 Antonio. He holds medical licensure in a number of
- states. He's certified by the American Board of

- Pediatrics, by the Board of Infection Control, and the American College of Epidemiology.
- He was admitted to the state bar of California in 1993 and maintains a current legal license. Prior to joining FDA, Dr. Wilson worked in regulated industry for over 20 years, holding senior positions in both regulatory affairs and drug safety.

8 So thank you, Dr. Wilson.

g (Screen.)

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## POST-MARKETING MONITORING OF VACCINE SAFETY

DR. WILSON: I want to spend a few minutes today reviewing the safety surveillance system that is currently in effect for vaccines, and also give you an idea of where we're moving in the near future with post-marketing surveillance.

16 (Screen.)

I think it's important just to remind you of
the legal basis for vaccine surveillance. The
seminal law is the National Childhood Vaccine Injury
Act of 1986, which actually established the Vaccine
Adverse Events Reporting System, known as VAERS.
This mandates reporting of adverse events on vaccine

- injury table in order for physicians to have
- $_{\rm 2}$   $\,$  coverage, and additionally accepts the spontaneous
- 3 reports from all other sources, and also the reports
- that are required to be submitted by manufacturers.
- So, very similar to AERS, with the proviso
- that we also have a bit of what I would call enhanced
- 7 reporting by physicians that is not a component of
- 8 AERS.
- We're also subject to 21 CFR 600.80, which
- is the same for therapeutic biologics for safety
- 11 reporting.
- 12 (Screen.)
- In addition, the FDA Amendments Act, as you
- all well know, gave additional authorities to the
- agency, specifically to require post-marketing
- studies and clinical trials, requiring sponsors to
- make safety-related labeling changes, and requires
- sponsors to develop and comply with REMS.
- 19 (Screen.)
- Significantly, FDAAA also requires the
- 21 establishment of active population-based
- surveillance, and I will be speaking a little bit

about what that means for vaccines.

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In the Office of Biostatistics and Epidemiology, we began an initiative in 2008 called Safety Throughout the Lifecycle. This initiative specifically was to enhance the use of statistical, epidemiological, and risk assessment and modeling methods for the evaluation of safety, expand and improve utilization of health care data to increase the power, speed, and quality of product safety monitoring after licensure.

It's important to realize that the other thing that we're responsible for in OBE for CBER is the blood supply, all blood components, as well as blood-derived products, just to put this in some perspective for you.

(Screen.)

Our vision for post-marketing safety monitoring for vaccines is that all patients' vaccine exposures and health outcomes are immediately and continuously accessible in automated databases, allowing optimal detection and analysis of potential

problems in biologics safety. We are nowhere near there yet, but I think we have made significant progress along this line during the past year, and we are hoping to make significant strides in the next two years with our current plans -- and budgets permitting, I might add.

7 (Screen.)

A little bit about VAERS. I think you're 8 familiar with AERS. There's not a lot of difference 9 here. This is the passive surveillance system. 10 is co-administered by FDA and CDC. I think another 11 theme that's very important for you to realize is 12 that vaccine safety monitoring is multi-agency. The 13 CDC plays a very, very important role. The National 14 Vaccine Program Office in Health and Human Services 15 So you will see that it is plays a role. 16 not strictly an FDA-focused activity. 17

is obviously by Reporting paper or 18 electronic formats, standard format. This is very 19 similar to AERS. We use MedDRA coding. The one 20 thing is that all serious AEs that come in 21 vaccines are reviewed daily by our medical officers. 22

So we have very much of a real-time emphasis on reviewing these reports.

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Now, the strengths I think are obvious. It's open-ended for hypothesis generation; very good for new or very rare events. It's timely. You have geographic diversity and you have the capability to monitor production lots. We do have electronic lot distribution data, and we can see whether or not there's clustering of events in lots.

There are clear limitations and these are I think pretty obvious to all of you. But I do want to point out that, for the purposes of what comes before this committee, in most circumstances, given the one-year cutoff for data, often all you're going to hear is VAERS data. There are some exceptions, and today is going to be one of those exceptions. I think you're going to see a little bit more of a panoply of reports today.

But as I talk about some of these other systems, it takes time for the data to mature in them and therefore it is usually after a year before we

have meaningful population-based data.

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Now, this schematic is just useful to show you how we think about it. We talk about signal detection, of which VAERS is the primary tool, the strengthening of signals, their validation, and then the formal hypothesis testing.

I put standard Sentinel out here to the side and I'm going to talk a little bit more about Sentinel in a few minutes. But before we get to Sentinel, I want to talk a little bit about some of the vaccine safety surveillance tools that are already in place.

14 (Screen.)

Probably the most important is the Vaccine Safety Data Link, which is managed under contract with the Centers for Disease Control and Prevention.

There are eight geographically diverse health maintenance organizations that participate in the large linked database that tracks vaccination, exposures, outpatient, emergency department, hospital and laboratory data, which are the health outcomes of

- interest, demographic variables that are potential
- 2 confounders. It includes roughly 3 percent of the
- 3 U.S. population right now. It's just about 9 million
- 4 in VSD. And clearly you can also do formal
- 5 hypothesis testing.
- So this is a very, very important tool for
- 7 vaccine safety.

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- 8 (Screen.)
- Now, what are the advantages? I think some 9 of them are I'm sure very obvious to this group. All 10 medical encounters are available at most sites. Wе 11 actually calculate true background rates of 12 various conditions of interest. We do have the 13 availability of medical charts, and it is available 14 for urgent studies, but I want to make sure that you 15
- It still takes time, and I think this is probably one of the hardest things that we have to deal with and that can be frustrating, is that even though this is electronic data, people have to have had the exposures, there have to have been enough of them, and you have to get the data. The initial work

understand that "urgent" does not mean immediate.

is all in the claims base part of the data, and then

 $_{2}$  we have to go back to the medical part for

3 confirmation.

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So, limitations. Sample size. In general 5 in vaccine safety, we're dealing with very rare 6 events. For instance, Guillain-Barre, that should be 7 actually -- it's one to two per million per year, not 8 100,000. We deal with events of this order of 9 magnitude. We're trying to detect the one in a 10 million, because this has very important implications 11 for public health perception of safety. Remember, in 12 general we're giving these to healthy individuals. 13

There's a lack of demographic and socioeconomic diversity in the HMO practices. It is a very homogeneous group, by and large, in these HMOs.

There's variable accuracy of the coded data used for the studies. These are claims base data.

Over the years some of these codes have been well validated. We know we can use them. In other cases, we have to go back to confirm that what's been coded

1 really comports to medical reality.

The unvaccinated population may be small for comparison. And it takes time to initiate these studies and to get results. Having said all of this, this is a powerful tool.

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Now again, how do we work together? Because I think it's very important for this committee to understand that this is complex. With CDC and HHS and many other agencies, we work closely together on vaccine safety surveillance activities. For example, VAERS is co-managed, the VSD is run by the CDC. Another example is that, although we do the labeling for vaccine, how a vaccine is used in practice is determined by CDC, and they rely on the Advisory Committee for Immunization Practices, who makes the recommendations for how the vaccine should be used in the American population, and then CDC takes that advice into account.

The vaccine data sheets that many of you are familiar with, that are written in lay language, is actually done by the CDC, and that is their

- 1 responsibility under law.
- 2 We have to work very carefully together and
- 3 coordinate this. In addition, to give you another
- example, there is an overarching committee at the
- 5 level of Health and Human Services that is the
- 6 National Vaccine Advisory Committee, that really
- advises on overall national policy on vaccines. That
- 8 committee is served mainly by the National Vaccine
- 9 Program Office.
- 10 So it's multiple layer, multiple agency,
- which makes our lives interesting.
- 12 (Screen.)
- Now to talk about Sentinel. I'm sure you've
- all heard about Sentinel because this is FDA-wide.
- 15 It certainly is -- the purpose is to develop an
- active electronic safety monitoring system so that we
- 17 can better monitor post-marketing performance. It
- augments, it doesn't replace, existing systems and
- enables us to have access to automated health care
- data by partnering with data holders.
- 21 (Screen.)
- So safety issues may be identified and

evaluated in near-real-time, and this is the potential of Sentinel. I'll talk a little bit about how we're trying to evaluate this for vaccines.

Sentinel expands the capacity for evaluating safety issues. You have improved access to certain subgroups and special populations -- children are certainly one of those -- improved precision of risk estimates due to an expanded number of populations available for study. And active surveillance may identify the increased risk of common AEs.

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development of Sentinel Now, the is proceeding, first with what is now known as mini-Sentinel, which is already under way and It consists mainly of a coordinating functional. center working with FDA in planning. The ultimate concept is, think of the coordinating center as an analytic unit and a brokerage who are presented with questions that need answers. They call resources of the Sentinel data partners. They create the necessary programs to get the data and to answer the questions.

So this is an area that has been under intense development. It is not -- mini-Sentinel is now operational, and we are participating in this process in CBER.

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This is just a list of some of the organizations that are involved. If you will notice, it does include pretty much everybody that's in VSD as well. They're a part of the Sentinel network, because a large number of the Kaiser HMOs make up a part of that network.

12 (Screen.)

What are the data environments available?

About 60 million individuals are covered, in mainly administrative and claims-based kinds of data. About 10 million of those have electronic medical records available. We have not yet fully exploited -- and that's part of the exploration that's going to be done, is how useful is access to these EMRs going to be and how do we make that happen.

Some 88 inpatient facilities, and there are device and disease registries that are also part of

1 Sentinel.

2 (Screen.)

Now, I want to turn to what is specific for 3 vaccines and is currently ongoing. We know it is "PRISM" because I can never remember "Post-licensure 5 Rapid Immunization Safety Monitoring System," which 6 is what it stands for. This was created during the 7 midst of the H1N1 pandemic and funded by FDA. 8 until the beginning of this fiscal year, the 1st of 9 October, it was being run by the National Vaccine 10 Program Office, with FDA and CDC participation. 11 is now under FDA and we're now not only funding it, 12 but actually managing it. It is now under the mini-13 Sentinel initiative. 14

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Now, before we go to this I'll just talk a little bit about PRISM. PRISM was created for the pandemic and the important part of PRISM is not only is it the large linked claims-based data. It was also the integration of vaccine registries. This became important because what they found during the H1N1 pandemic is that about half of the vaccinations

- that members in these insurance groups got would have been missed had they not been able to link with state
- yaccine registries to pull this information in.
- So I would call the unique piece of PRISM is really the involvement of state-run vaccine registries in addition to these other data sources.
- In addition to the Sentinel initiative, we have many other relationships with federal partners that are focused on vaccines. We are already doing near-real-time monitoring for Guillain-Barre syndrome for influenza, have been doing it now for a few years, and using Medicare data. This is an ongoing process.
- We are now exploring expanding this to other

  outcomes of interest for possible near-real-time

  surveillance also using Medicare claims-based data.

  Obviously, this is of interest for the elderly

  population.
- The other comprehensive data sets that are available for your real-time monitoring which we are now in the process of doing exploratory analyses, and some of this was done during H1N1 and is continuing

- this year under separate contracts, include studies
  with the Indian Health Service, the Department of
  Defense, and Veterans Administration.
- We now have studies ongoing with all these specifically for vaccines. The Indian Health 5 Service is probably one of our most interesting 6 relationships in terms of the pediatric population. 7 They have approximately 1.8 million enrollees, a 8 large percentage of those children. They have a very 9 sophisticated electronic health records system, and 10 they do have a national data warehouse where all of 11 this stuff is available. So we've been working 12 closely with them and developing are 13 relationships with them and are planning further 14 studies with them for vaccine outcomes. 15
  - We're hoping that this will add to the current population available in VSD a more at-risk, vulnerable pediatric population that may offer us additional insights for certain childhood vaccines.

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Again, we have other collaborations ongoing, and specifically doing a lot of work on methods

exploration, trying to use these large data sets. 1 is not necessarily the techniques that have been used 2. in the past. Statistically new techniques have to be 3 developed, they have to be validated. You have to be 4 -- near real-time surveillance sounds easy, 5 methodologically can be quite challenging. So we are 6 also spending a fair amount of our efforts in trying 7 to validate new methodologies that can be used. 8

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We work with our partners to coordinate topics for study and to minimize duplication. We have regular monthly meetings with CDC. We discuss safety signals that we are discovering. They talk about what they are -- inquiries they are receiving from states, and we coordinate our signal evaluation and research efforts.

(Screen.)

Finally, talk a little bit about Analytic Epi and Genomics Evaluation, our newer parts of our organization. Analytic Epi was formed in 2008, and this group is specifically defined as becoming familiar with and working with these large data sets

and in developing these relationships with our federal partners and mini-Sentinel.

The genomics team is a small group and what we're really focusing on is identifying possible human genetic contributions to adverse reactions, and we have a couple of studies ongoing now with MMR, so that this is an area where we're working closely with the NIH. But what we're interested in are what are the safety implications and potentially labeling and regulatory implications of these things for vaccines.

(Screen.)

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So in summary, I think the FDA Amendment Act has placed increasing emphasis on safety for the lifecycle, which we adopted as our strategic initiative. New tools and databases will allow us to migrate from reliance exclusively on passive surveillance to the use of population-based systems.

We're certainly exploring genomics to see if we can improve safety, and we're really trying to work toward an integrated approach of safety monitoring throughout the product lifecycle.

Thank you.

- 1 (Screen.)
- 2 My acknowledgments to a very large group who
- have been involved in this. Thank you all.
- 4 CHAIRMAN ROSENTHAL: Thank you very much,
- 5 Dr. Wilson, for that update.
- 6 We're running a bit behind, but I don't want
- 7 to miss an opportunity for people to ask questions of
- 8 Dr. Wilson while we have him at the podium. Any
- questions? Dr. Notterman.
- DR. NOTTERMAN: Thank you for a really
- 11 terrific summary of this outstanding and exciting
- work. I have what I think is probably a naive
- question, and that has to do with protection of
- 14 participants' private health-related information. I
- notice that you have access to medical records. I
- 16 assume you mean electronic health records. And
- 17 there's an effort to link this to genetic
- information. How do you assure that participants in
- this process have given their informed consent for
- their contribution?
- DR. WILSON: First of all, in terms of our
- genetics work, all of that so far is basically -- we

- do not directly access those records. We usually
- keep that, all the private information, behind a
- firewall and we get de-identified information that
- d complies with HIPPA.
- 5 We go out of our way to make sure that there
- is -- if necessary, there is informed consent. But
- 7 the most time we are able to use -- because we're not
- at the point of trying to look at specific patients
- 9 necessarily, but really looking at population-based
- 10 issues. We try to use de-identified data whenever
- possible.
- Part of the way Sentinel is set up is for
- that information to stay behind the data firewall and
- for us to basically receive reports, as opposed to
- 15 individual information.
- But to the case of where we ever get to that
- 17 point, it would absolutely require all of the
- 18 protections of informed consent.
- 19 CHAIRMAN ROSENTHAL: I couldn't tell whether
- Dr. Wagener or Dr. La Russa had their hand up. Dr.
- 21 La Russa.
- DR. LA RUSSA: Just a comment. I wanted to

- 1 mention two additional partners with the CDC in
- looking at vaccine safety issues. One is the group
- of six CSR centers, which is also funded by the CDC,
- and we often work in conjunction with VSD and with
- 5 VAERS looking at issues.
- The other agency that actually has been very
- helpful is the Department of Defense's vaccine safety
- g unit, which is run by Renata Engler. In answer to
- Ann's question, we often get VAERS reports to look at
- in the CSR centers, and unless we're going to be the
- 11 CSR center that's contacting the individual for
- additional information, all of the identifiers are
- 13 marked out. So we look at them as blocks with a
- diagnosis, with no names, and if we need to go back
- to them somebody else will go back to them.
- DR. WILSON: I apologize for not mentioning
- everybody. I do think the take-home message is that
- there are a lot of people involved, worried about and
- trying to have oversight of vaccine safety.
- 20 CHAIRMAN ROSENTHAL: Dr. Wolfe and then Ms.
- 21 Celento.
- DR. WOLFE: Very good presentation, I agree.

You didn't mention any outside of United States organizations. I was asked to give a talk earlier this year in Toronto, where there's an organization called ISES, Institute for Clinical Evaluation Studies. They have essentially the entire Ontario single-payer database.

You mentioned, quite properly, that in the VSD one of the problems, because you're into HMOs, is a lack of heterogeneity in the population. Just a suggestion, that using some of these databases that are very, very heterogeneous, such as all of the province of Canada, of Toronto -- of Ontario, rather -- might be a good idea. And there are probably other. I know that Quebec and I believe British Columbia also have those kinds of data sets.

DR. WILSON: I didn't go into the international. That's probably another hour. We've got a fairly large effort ongoing now in working with Europe and Canada, and we just had a meeting with Health Canada two weeks ago talking about this. We've been working very closely with the European Union, and as a matter of fact the head of our

- 1 Analytic Epi Branch has been working very hard on
- setting up, working with WHO and through WHO,
- 3 international collaboration on being able to do rapid
- studies of vaccine adverse events globally, including
- 5 developing countries.
- DR. WOLFE: Thank you.
- 7 CHAIRMAN ROSENTHAL: Ms. Celento, and then
- 8 we'll move on to the next speaker.
- MS. CELENTO: I guess I have a question
- about the selection of topics for study. Will this
- committee be hearing anything at any point about the
- 12 H1N1 vaccine, especially now that it's been
- incorporated into the ongoing seasonal flu vaccine?
- DR. MURPHY: I honestly don't know the
- answer to that, because I'd have to go see if it
- triggered anything, and I don't think it did. I
- don't think it did. So it probably will not come
- 18 back.
- But I'll use this opportunity to say to the
- 20 committee, I'm sitting here having data envy. This
- is as good as it gets. For vaccines we have this
- enormous infrastructure in place. We had a meeting

- in September, a two-day meeting talking about
- 2 pediatric safety and the limitations of our ability
- 3 to get information and what can we do to improve it.
- Ann McMahon was one of the people who directed a
- 5 panel.
- We invited all of these people who run these
- 7 large databases and had Sentinel there. They are
- doing a mini-Sentinel program right now for
- 9 pediatrics, and maybe, Ann, we'll have you present
- that to the committee some time in the future.
- DR. McMAHON: I'd be happy to.
- DR. MURPHY: I just think when you see these
- numbers and you see this infrastructure, just realize
- this is as good as it's going to get as far as
- adverse event monitoring. I think what you're seeing
- and having presented to you is something that's
- evolved over the years and I think is a wonderful
- 18 cooperative process at many levels of the government.
- So no, we're not going to do H1N1, it
- doesn't sound like. I'll follow up if I'm wrong on
- that. And, gee, this is a wonderful opportunity to
- 22 be able to hear all of this information. Thanks to

- 1 you all in CBER for taking the time to lay this out
- 2 to the committee.
- DR. WILSON: And I didn't mention the fact
- $_{
  m 4}$  that we do require sponsors to do rather large
- studies, and you'll be hearing about that in a few
- 6 minutes.
- 7 CHAIRMAN ROSENTHAL: Thank you, Dr. Wilson.
- DR. WILSON: Thank you.
- 9 CHAIRMAN ROSENTHAL: Our next speaker is Dr.
- 10 Jeff Roberts. Dr. Roberts is a medical officer in
- 11 the Division of Vaccines and Related Product
- 12 Applications at FDA's CBER, Office of Vaccine
- 13 Research and Review. Dr. Roberts attended medical
- 14 school at the University of Alabama, trained in
- obstetrics and gynecology at the University of
- 16 Colorado Health Sciences Center. In a fellowship at
- 17 the National Institutes of Health, Dr. Roberts
- 18 performed basic research on HPV focusing on animal
- 19 modeling of HPV infection.
- During his time at the FDA, Dr. Roberts has
- reviewed a wide variety of vaccines, but he continues
- to be focused specifically on HPV. As team leader in

- 1 the Division of Vaccines and Related Products
- 2 Applications, he manages the clinical review of the
- 3 licensed HPV vaccines and those in clinical
- 4 development.
- Dr. Roberts, thank you for joining us today.
- 6 PRE-LICENSURE SAFETY DATA: GARDASIL
- 7 (Screen.)
- DR. ROBERTS: Good morning. Thanks for that
- g introduction. I'm here to give you a brief overview
- 10 of the safety data accrued in the clinical
- development program for Gardasil.
- 12 (Screen.)
- Gardasil is prepared from virus-like
- particles, or VLPs, from each of the four HPV types,
- 6, 11, 16, and 18. As with many other inactivated or
- protein sub-unit vaccines, it's adjuvanted with an
- aluminum salt, in this case 225 micrograms of an
- aluminum sulfate. The dosing regimen is zero, two,
- and six months by intramuscular injection.
- 20 At the time of the initial licensure in
- 21 2006, the indication was for females 9 through 26
- years of age, for the prevention of the following

diseases caused by HPV-6, 11, 16, and 18: cervical

2 cancer, cervical, vulvar and vaginal dysplasia, and

3 genital warts.

4 (Screen.)

Gardasil was subsequently licensed in 2008 for prevention of vulvar and vaginal cancer, and in 2009 the indication was extended to males,

specifically for the prevention of genital warts.

In a moment Dr. Nguyen will discuss these licensing actions and which data on this time line will be the primary focus of discussion for this committee. What I will do in this presentation is to briefly summarize the data submitted in the initial licensure application.

15 (Screen.)

At the time of the initial BLA submission, the total safety population was drawn from 12 randomized, controlled studies involving over 21,000 subjects 9 through 26 years of age and about 13,000 of those received Gardasil. There were two studies that enrolled pediatric subjects. Both were immunogenicity and safety studies. 016 enrolled 10

- $_{1}$  to 24 year olds and 018 enrolled 9 to 15 year olds.
- 2 So the total number of pediatric Gardasil recipients
- was 3,430.
- In a moment I'll focus particularly on study
- 5 018.
- 6 (Screen.)
- 7 Study design in terms of safety surveillance
- was very similar across these studies. Generally,
- g safety assessments were done every three to six
- nonths after the vaccination series and through the
- end of the study. Most of the studies were three to
- four years, but some have long-term follow-up that is
- as long as ten years in the case of study 018.
- About half the subjects in the total
- population were included in a, quote unquote,
- 16 "detailed safety population." These subjects were
- given a vaccine report card and they were instructed
- 18 to record oral temperature after five days,
- 19 injection-site adverse events to 14 days, and
- 20 systemic adverse events to 14 days.
- 21 (Screen.)
- Here is the overview of safety during the

- first two weeks following any vaccination. This
- 2 represents the detailed safety population. So to
- orient you, the first column is the Gardasil group,
- 4 the second column is control, and these are the
- 5 percentages of subjects with the indicated
- 6 experience.
- 7 At the top, under the total rates of adverse
- 8 experiences, I've highlighted in blue the subsets of
- 9 injection site and systemic AEs. This was a theme
- 10 common to all these studies, that the rate of
- 11 injection site AEs was slightly higher in the
- Gardasil group, but the systemic AEs were relatively
- 13 balanced.
- 14 At the bottom, two of the most important
- outcomes are also highlighted in blue. So there were
- no imbalances in the rates of serious adverse events
- or deaths.
- 18 (Screen.)
- This is an accounting of every death that
- occurred during the entire study period in all the
- subjects in the pre-licensure data. This double
- asterisk denotes the subjects who were less than 18

- 1 years of age.
- 2 (Screen.)
- So I thought it would be useful to focus
  with a little more detail on study 018 because this
  was the most important study in adolescents from a
  safety perspective. This was a randomized, placebocontrolled, double-blinded trial in 9 to 15 year old
  subjects, and they randomized two to one to receive
  Gardasil or saline placebo.
- The targets for enrollment were stratified by gender and age, so that the final numbers achieved are displayed here.
- 13 (Screen.)
- The safety outcomes in this study were similar to those that were seen in the other studies.

  Again, there was an imbalance in the rates of injection site AEs, but not in systemic AEs.
- 18 (Screen.)
- Displayed on the bottom row are the rates of new-onset medical events during the vaccination period. This is representative of the other analyses in that there was no imbalance in the rates between

- these groups.
- In addition, there were no deaths in the
- 3 study. Five serious adverse events occurred in the
- Gardasil group, but each was assessed, both by the
- investigator and by CBER reviewers, as being unlikely
- to be related to vaccination.
- 7 It was noted that the injection site AEs
- 8 were mostly mild to moderate and that none of the
- 9 serious adverse events were related to local
- 10 reactogenicity.
- The conclusion was that the safety profile
- in adolescence is comparable to the safety profile in
- older subjects.
- 14 (Screen.)
- Also worth noting briefly is the pregnancy
- outcomes. Obviously, this is only a very small
- 17 subset of all the different obstetric and neonatal
- outcomes that were analyzed. At the bottom of the
- 19 table, I've displayed a couple representative
- analyses, live births and fetal loss. As with other
- outcomes, there were no notable imbalances.
- The exception was the rate of congenital

- anomalies, particularly those with an estimated date 1 of conception within 30 days of vaccination. 2
- review and discussions therefore focused particularly 3 on the case splits for congenital anomalies.
- With regard to this issue, CBER reviewers, 5
- group panelists, and a of independent 6
- teratologists blinded to the intervention 7
- similar observations: The widely divergent pathology 8
- among the cases did not suggest a pattern or 9
- syndrome; the findings were consistent with commonly 10
- observed anomalies; no signal for teratogenicity was 11
- apparent in the pre-clinical reproductive toxicology 12
- studies; vaccine exposure was temporally remote from 13
- the gestational critical period in each case; and the 14
- rate of anomalies consistent overall was with 15
- expected background rates. 16
- The conclusion therefore was that the data 17
- did not support a safety signal with regard to 18
- congenital anomalies. 19
- (Screen.) 20

- conclusion, no safety signal In was 2.1
- identified in the data submitted in support οf 2.2

- licensure, and this was the conclusion of the review
- of both the overall data set and the data in
- 3 adolescents. And continued safety evaluation in a
- larger population, through post-marketing studies and
- 5 other pharmacovigilance activities, was recommended
- and is being conducted, as you will hear about.

7 (Screen.)

- g I'd like to just acknowledge Nancy Miller
- 10 and Michael Nguyen for their help with this,
- particularly Dr. Miller, who was the CBER clinical
- 12 reviewer at the time of the initial licensure
- 13 application.
- 14 CHAIRMAN ROSENTHAL: Thank you very much,
- Dr. Roberts.
- Questions for Dr. Roberts regarding the
- material that was just presented? Yes, Dr. Farrar.
- DR. FARRAR: The congenital anomalies, do
- you happen to know what they were? Were they like
- 20 cleft palates or something?
- DR. ROBERTS: Yes, I do, if I can get back
- there.

(Screen.) 1 Here we go. They're listed. 2 Oh, okay. DR. FARRAR: 3 ROBERTS: So there were five: 4 dysplasia, pyloric stenosis, congenital 5 hydronephrosis, club foot, and congenital megacolon. 6 a little bit of follow-up, as 7 remainder of the safety data came in in the pre-8 licensure studies we subsequently reviewed, there was 9 another congenital anomaly on the control group. So 10 in the end the split was five to one. 11 CHAIRMAN ROSENTHAL: Other questions? 12 I'm not even sure I would DR. FARRAR: 13 consider pyloric -- this was pyloric stenosis when? 14 I mean, usual garden-variety? I mean, I'm not sure 15 that would be considered a congenital anomaly. 16 CHAIRMAN ROSENTHAL: Yes, Dr. Shwayder. 17 DR. SHWAYDER: What is the background 18 scatter of congenital anomalies in live births here 19 in the United States, what percentage? 20 DR. ROBERTS: I wish my wife was here. 2.1

DR. SHWAYDER: One percent, two percent?

- DR. ROBERTS: She's a CBER medical officer
- and she recently looked very closely at this, and I
- g can't pull it up off the top of my head. But I'm
- 4 thinking --
- DR. SHWAYDER: I think my colleagues over
- there might know the answer.
- 7 CHAIRMAN ROSENTHAL: Anyone from the panel
- that might want to venture an educated guess?
- g It depends a little bit on how you define
- them, but anywhere from one to a few percent.
- 11 Certainly all of these anomalies that are listed
- you'd expect to find -- with the exception of the
- congenital megacolon, you'd probably expect to find
- at least one in 10,000 live births.
- DR. MURPHY: Geof, we have someone else.
- DR. BEST: Hi. I'm Jeanine Best from the
- 17 Pediatric and Maternal Health Staff. The background
- rate of congenital anomalies in the U.S. population
- ranges from three to four percent, and that's
- regardless of any exposures.
- CHAIRMAN ROSENTHAL: Yes, Dr. Cope.
- DR. COPE: I used to study birth defects

- when I was at the National Cancer Institute. I think
- it might just be worth mentioning, too: Just as it's
- 3 stated, these are anomalies, so these are not
- $_{m{arphi}}$  defects. So it wasn't the organogenesis. It was --
- a lot of these are dysplasias, where it didn't finish
- off, rather than a defect in the organ itself.
- 7 CHAIRMAN ROSENTHAL: Yes, Dr. La Russa.
- DR. LA RUSSA: So I guess the reason why
- 9 we're asking this is that -- was a different
- definition used, because the control population has a
- 13.5 percent rate. So how is that calculated based
- in the way you'd usually calculate a three to four
- percent rate? What was included or not included?
- DR. ROBERTS: Well, I think what Dr. Cope
- has pointed out is an important distinction. These
- 16 probably included any anomaly observed in the trial
- and was a much looser definition than perhaps some of
- these big databases that look at birth defects.
- DR. MURPHY: I think that's the best
- 20 explanation we probably can come up with, is that we
- tend to spread a wider net and not limit ourselves to
- 22 what may be considered counted in the background

- population numbers.
- 2 That gets to another way that we tend to
- look at adverse events, is that we tend to be much
- more inclusive than to slice and dice them. So
- 5 that's the only thought I can have for you, because
- 6 we'd have to go back and see what the actual
- directions were to the protocol.
- CHAIRMAN ROSENTHAL: Dr. Notterman and Dr.
- 9 Wagener.
- DR. NOTTERMAN: Just to return to that, if
- there were 11 congenital anomalies out of 9,120
- control subjects, that's a rate of .12 percent, not
- 13 13.5.
- DR. ROBERTS: Well, 800 pregnancies or 469.
- DR. NOTTERMAN: It's still not --
- 16 CHAIRMAN ROSENTHAL: Dr. Wagener, can you
- speak into the mike, please?
- DR. WAGENER: I was going to ask what the
- 19 13.7 percent was, because it's certainly not the
- 20 percentage of pregnancies, it's not the percentage of
- births, and it's not the percentage of live births.
- 22 CHAIRMAN ROSENTHAL: Actually, you know

- what. All the percentages in this table seem to be
- off, perhaps by there's a digit shift.
- DR. ROBERTS: Yes. These are the total
- 4 population, so the N's going to be the number of
- 5 pregnancies, I believe.
- 6 CHAIRMAN ROSENTHAL: So 11 of 1,000, though,
- 7 is --
- DR. NOTTERMAN: 1.34.
- 9 CHAIRMAN ROSENTHAL: Yes. So that's
- reassuring, right? That's reassuring that those who
- have received Gardasil don't seem to have such a high
- risk for congenital anomalies and neither do the
- 13 controls. So that's reassuring.
- Other questions for Dr. Roberts?
- DR. MURPHY: It's the same mathematician
- that did the one in 100,000 Guillain-Barre.
- 17 (Laughter.)
- CHAIRMAN ROSENTHAL: Any other questions?
- 19 (No response.)
- 20 CHAIRMAN ROSENTHAL: There are some
- scrunched foreheads, but no hands up. Okay, Dr. La
- Russa.

- DR. LA RUSSA: Again going back, does this
- 2 make sense? There were 900 pregnancies in each group
- and there were about 300 fetal losses, about a third?
- 1 Is that correct?
- DR. ROBERTS: It probably includes every
- 6 single pregnancy that was either detected
- biochemically or otherwise, and the rate of loss is
- 8 very high when you do that much surveillance. So
- that would be what I would expect.
- 10 CHAIRMAN ROSENTHAL: So this may include
- 11 pregnancy termination as well?
- DR. ROBERTS: Right, it's all losses.
- 13 CHAIRMAN ROSENTHAL: Dr. D'Angio.
- DR. D'ANGIO: The rate of fetal losses in
- detected pregnancies is about a third, so that's
- about right.
- 17 CHAIRMAN ROSENTHAL: Other questions or
- issues? (No response.)
- CHAIRMAN ROSENTHAL: Well, let's take a
- 20 break. We have one in the schedule. Let's reconvene
- at 10:25. That is 12 minutes from now.
- 22 (Recess from 10:12 a.m. to 10:23 a.m.)

1	CHAIRMAN ROSENTHAL: Before I introduce Dr.
2	Nguyen, I'd like Dr. Roberts to have the opportunity
3	to just correct a point of discussion from the last
4	question and answer session. So, Dr. Roberts.
5	DR. ROBERTS: We were looking at this slide
6	just after the presentation. I think it's harder
7	than it may seem to pack down a huge clinical
8	development program into ten slides. But this was
9	our mistake, so our apologies. If you look at
10	"estimated date of conception within 30 days of

vaccination, "the congenital anomalies 13.7 and 13.5,

that should be 1.37 and 1.35. That represents 8 over

-- 11 over 802, which is the number of pregnancies

15 I hope that clarifies it.

with known outcomes.

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17 CHAIRMAN ROSENTHAL: Yes. Thank you very 18 much for that clarification.

DR. ROBERTS: My apologies again.

CHAIRMAN ROSENTHAL: So let's move on now to Dr. Nguyen's presentation. Dr. Nguyen is a medical epidemiologist in the Vaccine Safety Branch of the

- 1 Division of Epidemiology at the Center for Biologics
- 2 Evaluation and Research. Dr. Nguyen attended medical
- 3 school at the University of Rochester and completed
- his pediatrics residency at Washington University in
- 5 St. Louis. He is a lieutenant commander in the
- 6 United States Public Health Service.
- 7 Prior to joining CBER in 2009, Dr. Nguyen
- was an epidemiologic -- was an Epidemic Intelligence
- 9 Service officer with the CDC.
- 10 Dr. Nguyen.
- 11 (Screen.)
- 12 GARDASIL (HUMAN PAPILLOMAVIRUS QUADRIVALENT
- (TYPES 6, 11, 16, 18) VACCINE RECOMBINANT)
- 14 (Screen.)
- DR. NGUYEN: Good morning. I'll be
- presenting the pediatric focused safety review today
- 17 for Gardasil.
- 18 (Screen.)
- This time line illustrates the three major
- regulatory milestones to date. On June 8, 2006,
- 21 Gardasil became the first FDA-approved vaccine
- against the human papillomavirus.

- On September 12, 2008, approximately two 1 years later, Gardasil was approved for the prevention 2. of vulvar and vaginal cancer. This minor label 3 change is the trigger for today's pediatric safety review. Notably, the addition of these two final 5 cancer end points did not alter the vaccine's target 6 population and did not result in any material change 7 to the recommendations for clinical use promulgated 8 by the ACIP. 9
- Finally, on October 16, 2009, Gardasil was
  approved for the prevention of genital warts in
  males.
- 13 (Screen.)
- Previously the CDC and the FDA had published a comprehensive safety review of VAERS data covering the first two and a half years of market distribution.
- 18 (Screen.)
- However, today's focus will be the one year following the approval of Gardasil's vulvar and vaginal cancer indications. In the future, FDA will return to the Pediatric Advisory Committee to present

on the results after the extension of Gardasil into males.

3 (Screen.)

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In the time frame of interest, there were 4 million doses approximately 7 distributed. 5 Comparatively, in the first 39 months since licensure 6 an estimated 27.8 million doses were distributed, and 7 approximately 75 percent of all of these were 8 administered in children 9 to 18 years of age. 9

There are two main objectives of today's safety review. In the first half, I'll review the background safety information of Gardasil in order to provide a context for its safety surveillance. I'll review the results briefly of the CDC-FDA published safety review, as well as key findings from two observational studies that were completed prior to the trigger for this PAC review, the VSD study and a post-marketing commitment by Merck. I'll also review changes to the prescribing information through the 12th of September 2008.

The second half of my talk, I will be focused on the one-year pediatric safety review

following the approval of the new indication. I'll

2 summarize the VAERS data among U.S. children age zero

3 to 16 years who were vaccinated in the one-year post-

approval time frame. I'll review the changes to the

5 PI during this time period and I'll describe the

6 planned and ongoing post-marketing studies.

(Screen.)

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Before I begin with the actual data, I want 8 provide a context for the vaccine's safety 9 surveillance. Gardasil's licensure marked 10 coincided, excuse me, with the introduction of a 11 large -- the first large-scale U.S. adolescent 12 Between May 2005 and June of immunization program. 13 2006, three new vaccines for adolescents 14 licensed, bringing the total to four: 15

Menactra, which is a vaccine against meningococcal meningitis; Boostrix and Adecel, which are combination vaccines for tetanus, diphtheria, and acellular pertussis; and Gardasil. These four vaccines created a new 11 to 12 year old routine vaccination platform. This new platform created new safety challenges for vaccine safety surveillance,

including a new background of adolescent diseases.

Where previously the majority of 2 immunizations were administered in infants, with 3 these adolescent diseases there were a limited number -- excuse me -- a limited knowledge of baseline 5 incidence. Complicating the review was also a new 6 concomitant medications, including set of 7 contraceptives and behavioral disease modifiers, such 8 as smoking. 9

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In this milieu there are also unique issues for Gardasil itself. Even though Gardasil is principally a cancer vaccine, its mechanism of action is the prevention of HPV, which is sexually transmitted, which brings up a host of issues related to adolescent high-risk behavior. Gardasil also initially had only a female indication, which has since changed.

Additionally, Gardasil was introduced in the midst of an existing and successful cervical cancer prevention program. You also had some difficult messaging for public health officials. It was prophylactic and not therapeutic. Its efficacy was

- only against a subset of oncogenic HPV types, and
- $_{\rm 2}$   $\,$  there was a significant lag between infection and
- 3 cancer onset.
- Finally, to tip things off, Gardasil was
- rapidly included into school-entry mandates.
- So in this environment, Gardasil did
- 7 experience stimulated reporting.
- 8 (Screen.)
- Additionally, I want to provide a framework for how we evaluate -- or the differences between
- sort of the infant backgrounds and the adolescent
- 12 backgrounds. There are certain conditions, like
- allergic reactions and anaphylaxis, which are common
- to both populations, but there are also others in the
- immediate post-vaccination period which are more age-
- specific, such as febrile seizures in infants and
- young children and syncope in adolescent patients.
- Also, when we view reports of death, there
- is a background of sudden infant death in infants in
- 20 comparison to adolescents, where the sudden death is
- often due to cardiac reasons.
- Additionally, physicians and patients will

often report adverse events that previously have been 1 associated with vaccines, such as intussusception, 2. but also a host of other types of conditions that are 3 believed to be associated -- that they believe would be associated temporally with the vaccine, such as 5 Kawasaki's disease and auto-immune conditions and 6 endocrine conditions. We believe that a lot of these 7 are reported because they are clinically complex, 8 and they tend to be immune-mediated, 9 pathophysiology is not well described. 10

So we term these conditions the conditions of special interest, and FDA and manufacturers place special emphasis on reviewing them. Even though they're conditions that normally present in the target population absent vaccination, coincidental onset after vaccination might raise concern for a causal link. However, the preponderance of evidence to date really concludes that there is no evidence at this point to suggest, at least with auto-immune conditions and endocrine conditions, that there's a link with vaccination.

(Screen.)

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Now for some data. In the CDC-FDA published 1 safety summary, this published safety review 2. consisted of the first two and a half years, where 3 approximately 23 million doses were distributed. Over 12,000 reports were reviewed, of which 5 percent were non-serious. The most frequent adverse 6 events reported were syncope, dizziness, nausea, 7 headache, and injection site reactions. The safety 8 profile described in these VAERS data are consistent 9 with the prelicensure data, with two exceptions. 10

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The first is syncope, where we saw approximately 1900 reports in the first two and a half years. 90 percent of these occurred on the same day of vaccination and over 50 percent occurred within 15 minutes of vaccination. 15 percent of those resulted in falls and 11 percent were falls with head injury, including 45 lacerations, 18 dental injuries, 17 contusions, 9 fractures, 9 concussions, and 5 intracranial hemorrhages.

The second observation is that there were also 47 venous thromboembolism reports. Because of the nature of passive surveillance, only 66 percent

- had sufficient information for review, and 32 percent
- had no identifiable patient. Among the reports with
- 3 sufficient information, the median age was 20 years,
- with a range of 15 to 39 years, and the median onset
- interval was 23 days, with a range of zero to 306
- 6 days.
- 97 percent of these VTE reports occurred
- after Gardasil alone and 90 percent had at least one
- hnown risk factor, including 20 who took concomitant
- 10 contraception, 10 with a preexisting coagulation
- 11 disorder, 7 with immobility for various reasons,
- including surgery; 2 were smokers, 2 were pregnant,
- and one had hyperviscosity syndrome.
- 14 (Screen.)
- Additionally, there were 32 reports of
- deaths in our published safety summary. 63 percent
- of these had sufficient information for review and 12
- had no identifiable patient. 70 percent received
- Gardasil alone and there did not seem to be a dose-
- specific pattern. There was 9 after dose one, 5
- after dose two, and 6 after dose three.
- The median age was 17 years, with a range of

- 12 to 26 years; and there was no clustering by age. 1
- The median symptom onset interval was 14 days, with a 2.
- range of 2 to 288. And the median interval from 3
- vaccination to death was about 14 days as well. 4

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19 percent of these reports were among 5 children less than 16 years of age, and those are 6 detailed below. As you can see, the reports of 7 deaths range from 12 to 16 years. Four of them had 8 autopsy reports. Again, when we looked at the causes 9 of death, we look in the context of what we commonly 10 see absent vaccinations. So it's not surprising to 11 see cardiac arrhythmia and cardiomyopathies there as 12 causes of death, as well as influenza B virus sepsis.

I mentioned before, I'm going to be reviewing two observations of safety studies. first is the Vaccine Safety Datalink, which Wilson spoke to you earlier about. The VSD was the largest active surveillance study for Gardasil Ιt used rapid cycle analyses for signal detection for nine outcomes. Between August 2006 and October 2009, the VSD monitored over 600,000 doses in females ages 9 to 26 years, of which about 400,000

- were in girls aged 9 to 17 years.
- No safety signals were identified for
- Guillain-Barre, stroke, appendicitis, seizure,
- 4 syncope, allergic reactions, pancreatitis, and
- anaphylaxis. I only put a note there for anaphylaxis
- 6 because that's the only one that did not use
- g sequential methods, but nevertheless there was no
- 8 signal, safety signal, identified.
- g Even for venous thromboembolism -- excuse
- 10 me. For venous thromboembolism, they identified a
- non-significant increased relative risk of 1.98 among
- girls age 9 to 17 years. Of these, there were 13
- 13 cases electronically identified and 9 were chart-
- 14 confirmed. Eight of the nine cases had at least one
- known risk factor, including smoking, contraceptive
- use, obesity, prolonged immobilization, and again
- 17 coagulation disorder.
- They noted a cluster of four cases
- 19 identified on days two to three days post-
- vaccination. The VST is planning a self-controlled
- case series to further evaluate this finding.
- (Screen.)

The second observational study I wanted to 1 review is Merck's regulatory commitment for a post-2. marketing study of Gardasil in females. This was 3 conducted in Kaiser Permanente California Northern and Southern between the dates of October 2006 and 5 March of 2008. A total of approximately 350,000 6 Gardasil doses were evaluated, of which 44,000 7 received three doses per protocol, which basically is 8 a stringent criteria, that they received it within 9 certain amounts within the vaccine schedule as 10 recommended. About 189,000 females received at least 11 one dose, with 51 percent of those age 9 to 15 years. 12

Please note that, because Northern California Kaiser Permanente is also in the VST, there are some doses administered that overlap with the VST data, but the exact number of doses is not known.

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This post-marketing study in females was
designed as a preliminary tool for detecting
potential safety signals. So no formal hypotheses
were tested. The methods were active surveillance
using ICD-9 codes to identify potential cases,

- followed by chart review to verify the exposure and
- $_{\rm 2}$   $\,$  the outcomes and if they occurred in the correct
- 3 sequence.
- For prevalent outcomes, a manageable random
- 5 sample was selected for case review, and the
- 6 comparison groups differed by the study component,
- and I'll review those right now.
- 8 (Screen.)
- There are three components to this PMC.
- There's the general safety, pregnancy, and autoimmune
- 11 conditions. In the general safety component, the end
- 12 points were all hospitalizations and ER visits
- occurring on days zero, 1 through 14, and 1 through
- 14 60 days after each vaccination. The rate of these
- hospitalizations and ER visits were compared to a
- 180-day post-vaccination self-comparison period.
- In the pregnancy exposure, they used active
- 18 surveillance for congenital anomalies and the
- comparison was published background rates.
- For the autoimmune conditions component,
- there were 16 pre-specified conditions, which are
- listed below, and they monitored for these pre-

specified conditions occurring within 6 months after
each vaccination, and they compared this to incidence
rates in the non-vaccinated group within the Kaiser
Permanente population.

(Screen.)

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The major findings in the general safety component was that they identified an elevated risk for syncope on day zero and possibly cellulitis on days 1 through 14, with an estimated 6.6 cases of syncope per 100,000 doses and 13.5 cases of cellulitis per 100,000 doses.

The "possibly" part of the cellulitis is that upon medical record review -- recall that these are identified from billing and then they go into the medical record and verify the exposure and they verify the outcome. What they noticed when they did that is that some of these cellulitis were not really associated with the injection site, and also had a paucity of clinical data to be able to verify this.

They did not detect an elevated risk detected for VTE or GBS, and there were no unusual patterns detected among the 14 deaths that were

- detected by ICD-9 coding. Those 14 deaths are listed below.
- In the pregnancy exposure, there were 3.6 3 percent rate of confirmed congenital anomalies among Gardasil-exposed pregnancies, compared to 5 background rate of 3.0 percent, and that 3.0 percent 6 talked about before as primarily from 7 general anomaly database metropolitan area in 8 Atlanta, run by the CDC. 9
- There was no elevated risk detected and there was no apparent pattern among any of these congenital anomalies, which were reviewed by an independent teratologist.
- For autoimmune conditions, 11 out of the 16
  pre-specified outcomes had new-onset cases. The
  others did not have any cases for evaluation, and
  there were no elevated risks detected.

18 (Screen.)

So I want to review the cumulative changes to the prescribing information from the time period of licensure up until the trigger for today's review.

In the adverse events section, nausea and dizziness

were added to the table and a brand new postmarketing experience section was added to the label,
as described here. I'm not going to go over each
individual one, but to note that each of these
changes to the PI were made primarily in response to
the VAERS data.

(Screen.)

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I do want to focus just a second on syncope as it's described in Gardasil's package insert, mostly because it illustrates how FDA reconciled the safety data that accumulated in the first two years.

Once we -- once it was realized that syncope seemed to be associated with vaccination, we put it in the label and also included a statement that patients should be observed for approximately 15 minutes after administration of Gardasil, in hopes to prevent much of the incidents.

As more data came in, we added additional warnings and descriptions that said that syncope was associated with falling, and then finally that syncope was associated with falling and injury.

(Screen.)

Additionally, the safety-related components of the package insert included contraindications and 2. pregnancies, none of which were changed in these two The only contraindication is to yeast, and the pregnancy section describes that Gardasil is not recommended in pregnant women, category B, and that physicians are encouraged to enroll their patients into a pregnancy registry. 

(Screen.)

So that completes the first half of the review, and I'll move on to the one, the post-approval review. Before I go there, I do want to take a moment to talk about how we, at a medical officer level, how we do signals detection in VAERS.

16 (Screen.)

We manually review all serious reports on a daily to weekly basis. We identify serious and unexpected adverse events. We create case series and analyze for unusual patterns and trends, and we generate periodic adverse event reports. As I mentioned before, we continuously monitor conditions

of special interest.

We also apply statistical methods to these 2 data, and we survey and review all VAERS the 3 published case reports and safety studies correlate these findings with manufacturer-provided 5 safety data. As Dr. Wilson mentioned before, we 6 collaborate closely with CDC on case review and 7 public messaging for vaccines. 8

(Screen.)

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So these are the numbers of Gardasil reports
in VAERS during the one-year period of interest. In
the table you'll see the columns are serious, deaths,
non-serious, total, with a division between the U.S.
reports and the total numbers. I'll be focusing on
these numbers here.

(Screen.)

So these are the two reports of deaths among children zero to 16 years of age during this one-year time frame. The first is a non-injection site necrotizing fascitis with septic shock. There were several concomitant vaccinations and this occurred in an 11 year old girl, whose blood culture eventually

- grew Strep pyogenes.
- The second is an unexpected death in
- g epilepsy in a 13 year old with preexisting seizure
- disorder.
- 5 We did not feel that these appeared to be
- f related to vaccination.
- 7 (Screen.)
- Additionally, we analyzed the most
- g frequently reported terms among serious reports in
- 10 children zero to 16 years of age. As you can see
- here, each of the MedDRA preferred terms has been
- listed in the prescribing information to notify the
- public about these events.
- 14 (Screen.)
- Similarly, we reviewed the most frequently
- reported terms for non-serious reports in this one-
- year time frame among children zero to 16 years of
- age. Again, you'll see a similar number -- excuse me
- 19 -- a similar description of the preferred terms that
- 20 come up in the serious reports. Each of these are
- 21 listed.
- 22 (Screen.)

just described these reports here. The only one that is not listed is cellulitis, and the rest are listed in the package label. Notably, for pulmonary embolism, since it was noted as a possible concern in VST, all of the pulmonary embolism reports had a preexisting risk factor.

(Screen.)

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I'll review the pregnancy registry data here only because the most recent update occurred within the one-year time frame that we are interested in. This is an ongoing five-year regulatory commitment by Merck, agreed upon in licensure. It's a prospective observational study in the U.S., Canada, and France, although the vast majority of data come from the U.S.

This includes interim data from June of 2006 to May of 2009. Of the 1,000 total vaccine-exposed pregnancies with known outcomes, there were 64 miscarriages, 24 congenital anomalies, and 10 fetal deaths. In the pediatric population, only one of the 64 miscarriages occurred in females 9 to 15, and 5 of the 24 congenital anomalies and 3 of the 10 fetal

deaths occurred in females less than 16 years of age.

The conclusion was that the overall rate of congenital anomalies and miscarriages was within the estimated background rate, and the review of the congenital anomalies and deaths did not identify any unusual patterns, and I'll take the next couple of slides to show you exactly the pediatric cases.

(Screen.)

These are the pediatric cases of congenital anomalies. They are atrial septal defect, gastroschisis, again ASD, polydactyly, and pulmonary stenosis. There is no mention of -- gastroschisis is not mentioned in prescribing information and, although Strattera has known cardiovascular effects, cardiac anomalies is not one of them.

(Screen.)

These are the three reports of fetal deaths in children less than 16 years of age. Each had concomitant medications and again there were no seemingly patterns to these fetal deaths.

21 (Screen.)

So these are the changes to the PI that

occurred in the period, the one-year period of interest. Again, syncope was modified from "may result in falling with injury" now to "sometimes associated with tonic-clonic movements and other seizure-like activity." The additional sentence that is associated syncope with tonic-clonic movements, the activity is usually transient typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position" was added, again to improve clinical understanding for physicians and health care providers, as well as for patients. Additionally, "chills" was added to the post-marketing section.

14 (Screen.)

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So the overall post-marketing surveillance framework is multifaceted and fairly sophisticated. The base of it is really the passive surveillance in VAERS and the pregnancy registry, although these two sources of data are not the strongest sources of the data. There is also active surveillance, which is much stronger in the fact that there's a defined populations and rates can be calculated, as well as

the fact that there's a comparison population. 1

there are long-term follow-up studies to address 2.

long-term outcomes. 3

(Screen.) 4

As I mentioned before, the safety study in 5 females and the Vaccine Safety Data Link have already 6 been completed. There is also a new study of safety 7 in males 9 to 26 years of age which is ongoing. 8 there are several additional studies for long-term 9 follow-up in women adolescents of vaccine-impacted 10

population and a long-term follow-up in males.

(Screen.)

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So this is just a brief table that describes the study design, the population, and the safetyrelated objectives. You notice that a lot of these are clinical trial extensions and are primarily focused around efficacy and effectiveness. However, there are some safety-related outcomes.

Also of note that it does cover a broad range of the indicated population, from 9 all the way to 26 years of age.

(Screen.) 22

So in conclusion, more than 600,000 doses of Gardasil have been actively monitored. An additional 135,000 doses will be actively monitored in the ongoing male study, for a total of seven ongoing post-licensure studies with safety end points.

There have been multiple safety-related changes to the prescribing information; and FDA will continue routine safety monitoring, as described.

Thank you.

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CHAIRMAN ROSENTHAL: Thank you, Dr. Nguyen.

Can I start the questions off by asking a few things about syncope. First, as I was looking through the material it looked like the reference group was, in the study that was described on one of the slides before 21, that the reference group, the comparison group, was selected differently for some of the different outcomes. I'm wondering if you can help me understand what the reference group was, what was the comparison group, when coming up with the syncope risk estimates immediately following vaccination.

DR. NGUYEN: I presume that you're talking

- about the post-marketing study of Gardasil in
- females; is that correct?
- 3 CHAIRMAN ROSENTHAL: Hang on. I think so.
- 4 Mention was made that there were different reference
- 5 categories for the different comparison groups.
- DR. NGUYEN: The finding of syncope in the
- 7 post-marketing study for females by Merck was in the
- general safety component.
- 9 CHAIRMAN ROSENTHAL: Yes.
- DR. NGUYEN: And this was -- so the end
- 11 points were all hospitalizations and ER visits in
- these three different windows after each vaccination.
- 13 The comparison group was a 180-day self-comparison
- 14 period.
- 15 CHAIRMAN ROSENTHAL: Okay.
- DR. NGUYEN: That began 91 days after dose
- three of Gardasil.
- 18 CHAIRMAN ROSENTHAL: So people were serving
- as their own controls?
- DR. NGUYEN: Yes.
- CHAIRMAN ROSENTHAL: Okay. Then I just had
- another general process question. Some of the events

- that were described, things like syncope, dizziness,
- 2 vomiting, showed up both in the context of serious
- reports and in the context of non-serious reports,
- and I'm wondering if you can speak to how that
- 5 distinction is made.
- DR. NGUYEN: Sure. Let me bring up that
- 7 slide before I begin.
- 8 (Screen.)
- GHAIRMAN ROSENTHAL: That is around slide
- 10 21.
- DR. NGUYEN: Yes. This is a good question.
- So why is headache both in the serious and in the
- non-serious most frequently reported terms? This is
- a function of how our passive surveillance -- how
- VAERS is set up, in the sense that each report has a
- one-to-many relationship. A single report will
- produce anywhere from 3 to 20 different MedDRA PT
- 18 terms. So when we do a frequency of the most
- 19 frequently reported terms, there can be multiple
- etiologies contributing to it.
- So let me give you an example. Headache may
- 22 be reported by someone who experienced principally

- flu-like illness as their main adverse event. It
- 2 could be related to syncope and they hit their head,
- 3 or it could be related to acute disseminated
- 4 encephalomyelitis. But all three of those reports
- 5 will contribute a PT term for headache, because it
- 6 was reported in the actual text verbatim.
- 7 So there is a one-to-many relationship to
- these reports, and that's one of the limitations to
- how -- to the MedDRA PT frequency.
- 10 CHAIRMAN ROSENTHAL: So if "dizziness" --
- well, let's talk about syncope. If "syncope" is
- listed under serious reports, then "syncope" was
- essentially the primary complaint?
- DR. NGUYEN: We don't have an ability in the
- VAERS data to pull out, to extract, what exactly is
- the primary complaint, unless you do manual reviews.
- DR. MURPHY: Maybe this will help. What if
- the headache was associated with something that
- qualifies for the regulatory term for "serious," like
- hospitalization, etcetera? Would that then put the
- headache on the serious list?
- DR. NGUYEN: That's correct.

- DR. MURPHY: Okay.
- DR. NGUYEN: If you go back to this slide
- here --
- 4 (Screen.)
- DR. NGUYEN: 19, the serious events include
- deaths, life-threatening experiences, inpatient
- hospitalization, prolongation of hospitalization, or
- 8 permanent disability -- excuse me, persistent
- g disability.
- 10 CHAIRMAN ROSENTHAL: So is that the only
- 11 distinction, then, that the symptom meets this
- 12 categorization?
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- DR. NGUYEN: The report, the overall report,
- meets that category, not the individual symptom. So
- 16 when you categorize this, if this is a serious
- 17 report, it contributes those PT terms. If it's a
- non-serious report, they contribute those PT terms.
- 19 CHAIRMAN ROSENTHAL: I got it, okay. Thank
- you for clarifying.
- A number of questions down my left. Dr.
- Wagener was first up, then Dr. Notterman, then Dr.

- 1 Wolfe. And Dr. La Russa, did I see your hand, too?
- 2 All right. Thank you.
- DR. WAGENER: So a quick question. There's
- an implication that was made that the reason that
- 5 syncope is being seen with this vaccine is because of
- the age group and it's predominantly female. Do you
- 7 have data from other adolescent-administered
- vaccines, such as meningococcal vaccine --
- DR. NGUYEN: We do.
- DR. WAGENER: -- within a similar age group
- and a similar gender, that would see whether or not
- this is a higher risk than those, or is it just
- 13 getting a shot?
- DR. NGUYEN: There's a couple ways to answer
- 15 this. The first is that we have -- in VAERS we are
- seeing that across the board in adolescent vaccines.
- 17 Syncope is associated with any noxious stimuli. In
- this case it happens to be a needle. We've also seen
- 19 it with blood donation. We've also seen it with
- other noxious stimuli, and it causes syncope,
- dizziness, and the falls.
- I can't tell you that -- in VAERS, because

- it's passive surveillance, I can't tell you that the
- 2 rates are any different, so I can't give you a risk
- g estimate. But when we look at -- so there's no
- 4 observational studies that have tried to compare
- these vaccinations head to head. I wouldn't be able
- 6 to tell you that.
- 7 CHAIRMAN ROSENTHAL: Next, Dr. Notterman.
- DR. NOTTERMAN: Thank you for an excellent
- g summary of this information. I want to turn to slide
- 10, where you cover the Vaccine Safety Data Link.
- DR. NGUYEN: Sure.
- 12 (Screen.)
- DR. NOTTERMAN: I'm particularly interested
- in the last bullet, with respect to thromboembolism,
- because that signal came up a couple of times.
- DR. NGUYEN: This gets a little complicated.
- 17 With the active surveillance method they use
- MAXSPRT. The MAXSPRT is a sequential analytic method
- that allows you to analyze the safety data as you
- 20 accumulate, so you can do this in real time. It
- accounts for the multiplicity of the looks at the
- 22 data.

- Before you initiate the study, you set a
- 2 critical value, which is sort of your safety
- threshold, and then the test statistic that you look
- at is the log-likelihood ratio, which is simply a
- 5 measure of observed to expected.
- So what you see in the results of the VSD is
- that no safety signal is identified for any of the
- nine outcomes. None of them signal by the definition
- of MAXSPRT. However, there was a non-significant
- 10 elevated risk of 1.98 that was identified, only in
- the females, in girls 9 to 17. In the adult
- population, it was not seen.
- DR. NOTTERMAN: So when you say it's non-
- 14 significant, do you have the estimates, the
- confidence estimates?
- DR. NGUYEN: Sequential methods don't
- 17 produce any confidence intervals. They produce --
- the main statistic is the LLR, the log-likelihood
- ratio. It's much more akin to a P value, where it's
- 20 either significant or not significant.
- DR. NOTTERMAN: So to what extent could this
- non-significance have been related to an absence of

- power or inadequate power? In other words, is it
- 2 possible that there actually is an elevated relative
- risk, but that the study was underpowered to find it?
- And do you have an estimate of the power to find a
- 5 true finding?
- DR. NGUYEN: The follow-up study is designed
- 7 to answer those questions. The answer is it
- g continues to be a possibility. However, having said
- g that, there are significant confounding factors,
- 10 which the self-controlled case series is meant to
- address, principally the preexisting coagulation
- disorders, as well as the contraceptive use.
- 13 Let me turn to --
- DR. NOTTERMAN: I was going to ask about
- that, because in a couple of slides you mentioned
- that many of the individuals who had thromboembolism
- $_{
  m 17}$  had confounding or coincident disorders. But you
- might expect to find those in the control population
- 19 also.
- DR. NGUYEN: Correct.
- DR. NOTTERMAN: There's nothing special
- about those. So I wouldn't want to say that --

- DR. NGUYEN: Not necessarily, because those
- who are vaccinated and those who are not vaccinated
- may be different populations. And those who are --
- DR. NOTTERMAN: But you haven't established
- 5 that they are.
- DR. NGUYEN: When you get vaccinated, it
- 7 presents -- it may be that they were vaccinated
- because they came -- And I'm speculating here -- that
- 9 they came for a health visit or specifically because
- they desired to be sexually active, and they're
- initiating oral contraception. We know that oral
- 12 contraception is a known risk factor for venous
- thromboembolism and that it's associated with a three
- to six time elevated risk compared to the baseline of
- non-users of oral contraception.
- So that there are significant confounding
- factors here that are in play.
- DR. WILSON: I think the answer to your
- question is there are going to be the self-controlled
- case series for the very reason that, yes, we're
- still concerned.
- DR. NOTTERMAN: Okay, that's good. Thank

- 1 you.
- Thank you, Dr. Nguyen.
- 3 CHAIRMAN ROSENTHAL: Dr. La Russa and then
- 4 Dr. Wolfe.
- DR. LA RUSSA: First a comment about this.
- 6 We were just discussing this. Can you just tell us
- y what the P value was around the 1.98?
- DR. NGUYEN: It's the log-likelihood ratio.
- The log-likelihood ratio was 1.51, with a critical
- 10 value of 3.2.
- DR. LA RUSSA: Just a comment. Anecdotally,
- 12 practicing pediatricians have told me that their
- impression is that the HPV vaccine hurts a lot --
- DR. NGUYEN: Yes.
- DR. LA RUSSA: -- and that's their
- explanation for the syncope. So whether this is just
- a phenomenon that mostly girls are getting vaccinated
- and it has nothing to do with the gender difference -
- 19 -
- DR. NGUYEN: And that was borne out in the
- clinical trials as well. That was very apparent,
- that pain was recorded at much higher rates.

- DR. LA RUSSA: The other thing I wanted to
- ask you about was, with the 11 year old girl who
- died, you mentioned the autopsy results and there was
- a necrotizing fascitis in the lower leg. In the
- autopsy report were there any findings at all at the
- 6 injection site?
- 7 DR. NGUYEN: No, no.
- DR. LA RUSSA: Okay.
- 9 CHAIRMAN ROSENTHAL: Dr. Wolfe.
- DR. WOLFE: This is parallel to Dr.
- 11 Wagener's question. In response to his question you
- pointed out that with this different demographic
- group several new vaccines are now being done in
- 14 adolescents, that there were other vaccines -
- meningococcal, whatever -- in which there were also
- syncope occurring.
- DR. NGUYEN: Yes.
- DR. WOLFE: On slide 15 you morph from
- 19 syncope following any vaccine, especially in
- 20 adolescents, and then mention Gardasil, to just
- Gardasil at the end of slide 15, and then in slide
- 22 27, back still to Gardasil.

So I guess the question is, if in fact, as 1 makes a lot of sense, whether the pain is the only 2. determinant or not -- and it sounds like the age 3 demographic is as much a determinant -- if there is evidence in that age group that vaccinations are more 5 likely to be followed by vasovagal as in syncopal 6 episodes, why did you not stick to the original 7 labeling? Or, parallel to that, is there labeling on 8 these other vaccines that are used in adolescents 9 that says syncope can occur? 10

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The 15-minute business makes sense, assuming that these injuries to the heads and so forth were outside the office. Sitting for 15 minutes in an office probably makes sense for any vaccination for any age. But why did you move away from the statement that said in this age population syncope can occur with vaccinations?

DR. MILLER: HIV-infected. My name is Nancy

Miller. I'm a medical officer. I just wanted to -
when we worked with our labeling consultants or

people at CBER, it was advised that we be specific

for the vaccine that we're labeling, not to

- generalize to any other vaccine, but we're talking
- for Gardasil. That's why it was said with Gardasil.
- DR. WOLFE: Do the other vaccines that are
- 4 used in this age group which you're saying have
- syncope, do they have the same kind of labeling?
- DR. NGUYEN: Yes, they're labeled for
- 5 syncope as well.
- DR. WOLFE: And with the 15 minutes, you
- g should wait for 15 minutes?
- DR. NGUYEN: I'd have to check on that.
- DR. WOLFE: Okay. It's just worth doing.
- DR. NGUYEN: Sure.
- DR. WOLFE: Because it sounds like a
- 14 reasonable phenomenon.
- 15 CHAIRMAN ROSENTHAL: Dr. Motil, then Dr.
- 16 D'Angio.
- DR. MOTIL: My question was answered
- 18 earlier.
- 19 CHAIRMAN ROSENTHAL: Dr. D'Angio.
- DR. D'ANGIO: My question was asked and
- answered earlier.
- 22 CHAIRMAN ROSENTHAL: Ms. Celento.

I had concerns about the VT MS. CELENTO: 1 events, so I appreciate that there will be further 2. study of that.

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- But I have a couple of overall concerns on labeling for this vaccine as well as any others. 5 have never been handed a label when my child's been 6 administered a vaccine ever. So unless I go on line 7 and find a label and read it before we go to the 8 pediatrician, how would I know as a consumer what any 9 of these? 10
- DR. WILSON: CDC -- this is where you've got 11 to understand the way it works. CDC is actually 12 accountable for the communication, and that's what 13 the vaccine summary sheets are supposed to be for. 14 They're the ones who control the content of that. 15
- We obviously supply them the label. Wе 16 obviously have some review in that process. But they 17 actually are the ones charged by Congress 18 saying, this is the information parents are supposed 19 to have. 20
- MS. CELENTO: I understand that, but you're 2.1 granting license of the sponsor to produce the drug 22

- and for it to be administered in a pediatrician's
- office, and there's a label that goes with it. And I
- 3 understand that CDC might have the responsibility for
- the education, but that's like saying I told my son
- to feed the cat and he didn't and the cat died.
- DR. WILSON: It's more than that. That's
- 7 the -- the practice actually is what they
- 8 communicate.
- MS. CELENTO: I also just want to note that
- the fact that death may occur is listed under general
- 11 disorders and administration, site conditions, in
- section 6.2, post-marketing experience. I understand
- that we haven't determined any of these deaths are
- 14 directly related, if there were preexisting
- 15 conditions, etcetera, etcetera. But I just have a
- real concern that the fact that death may occur is
- buried in post-marketing experience, and again under
- 18 general disorders and administration, site
- 19 conditions.
- DR. NGUYEN: Please keep in mind that we do
- have better data than VAERS, that I discussed a
- little bit about. When we do have a comparison group

- and we're actively monitoring, we don't see any association with death with Gardasil.
- 3 So the post-marketing section of the label
  4 is a funny section because the threshold to get in
  5 there is very low. Basically, the threshold is that
  6 it's, A, serious, B, important, and three, it's ever
  7 mentioned in VAERS. So it does not -- unfortunately,
  8 it's confusing and not well understood. It does not
  9 portend an actual -- a definitive proven risk for the
  10 medical product --
- 11 CHAIRMAN ROSENTHAL: Doctor --
- DR. NGUYEN: That's it.
- 13 CHAIRMAN ROSENTHAL: Dr. La Russa.

14

- Sorry. I didn't mean to cut you off, Dr.
- 16 Nguyen.
- DR. LA RUSSA: A comment and then a 17 comment is, while it's question. The the 18 responsibility of the CDC to develop the vaccine 19 information sheets, it's the responsibility of the 20 practicing physician who's giving the vaccine to 21 actually hand it to the parent. And that's something 22

- we need to be more vigilant that actually happens.
- The question goes back to syncope. In the
- $_{
  m 3}$  post-marketing study of Gardasil there actually is an
- elevated risk found for syncope.
- DR. NGUYEN: Yes.
- DR. LA RUSSA: So my question is is there a
- 5 statistically significant elevated risk found for
- 8 other vaccines given in that age group, or is it just
- g for Gardasil, which would explain why the labels
- 10 might be different?
- DR. NGUYEN: I'll answer your question in
- just a moment. Let me go back to Ms. Celento's
- 13 comment.
- There is a movement in FDA to modify the
- package insert to be more friendly and that is under
- 16 discussion.
- To address your question, I don't have head-
- 18 to-head comparisons. Again, we did detect an
- 19 elevated risk compared to a non-vaccinated
- 20 population, an unexposed population. So in that
- study we did identify an elevated risk. But there's
- no head to head for Menactra or TDEF.

- 1 CHAIRMAN ROSENTHAL: Dr. D'Angio, Dr.
- Goldstein, and Dr. Shwayder, in that order.
- DR. D'ANGIO: To get back to Ms. Celento's
- question, does anybody know what the vaccine
- information sheet says?
- DR. NGUYEN: Yes. I have it with me, I
- 7 believe. DR. D'ANGIO: Because I
- 8 think one of the questions that I'd have is whether
- 9 there's enough communication within the federal
- 10 government to make sure that consumers get the
- information, even if it is somebody else's job to
- 12 feed the cat. And if the VIS has that information
- 13 and the pediatrician gives it out, then that
- information is conveyed and probably conveyed in a
- form that's a little bit more friendly than the
- 16 package label.
- But if that's not in the VIS, then there's
- obviously a problem.
- DR. NGUYEN: I thought I brought it. I
- 20 didn't.
- 21 CHAIRMAN ROSENTHAL: So maybe one thing that
- the agency can take back is just that this issue came

- up and that the committee just suggests that, even
- though it may be outside of our scope, that the
- agency continue to liaise with CDC around
- d communication to families.
- DR. WILSON: We do. There is a formal
- 6 mechanism.
- 7 CHAIRMAN ROSENTHAL: We appreciate that.
- DR. WILSON: We do review the VISes. They
- g send them to us. We make our comments, and they
- 10 ultimately decide it. I do have the HPV VIS here in
- 11 front of me.
- 12 CHAIRMAN ROSENTHAL: Is the word "syncope"
- 13 on it?
- DR. WILSON: It reads "Other problems.
- 15 Fainting. Brief fainting spells and related
- symptoms, such as jerking movements, can happen after
- any medical procedure, including vaccination.
- 18 Sitting or lying down for about 15 minutes after a
- vaccination" -- this is all bolded -- "can help
- 20 prevent fainting and injuries caused by falls. Tell
- 21 your provider if the patient feels dizzy or
- lightheaded or has vision changes or ringing in the

- 1 ears."
- 2 CHAIRMAN ROSENTHAL: Wow. That sounds
- great. All right.
- DR. MURPHY: I think our lesson from today
- 5 is we will include that in your package in the
- future, not just the label.
- 7 CHAIRMAN ROSENTHAL: I think my sense is
- 8 that's fairly clearly communicated.
- 9 Dr. Goldstein.
- DR. GOLDSTEIN: I was just going to
- 11 reiterate for Ms. Celento the obligations of the
- practitioner in communicating this, and there's no
- oversight by the CDC or the FDA on what they do or
- they don't do.
- 15 CHAIRMAN ROSENTHAL: Dr. Shwayder and then
- 16 Dr. Wolfe.
- DR. SHWAYDER: I just have a plea. When you
- throw in something like death, you should say: And
- these four cases were probably related to something
- other than the vaccine, because on a daily basis I
- get mothers, like Ms. Celento, who say: Well, I'm
- not going to use that medicine because it causes,

- fill in the blank. And you look at the data and it's
- not related, and you realize that there's some
- obligation either from the FDA or whatever to cover
- your back side from the drug company and that it had
- 5 to be included.
- So it would be nice if you had some sort of
- 7 relative risk or other disclaimers put in there on
- 8 these high action words.
- 9 DR. NGUYEN: I agree.
- 10 CHAIRMAN ROSENTHAL: Dr. Wolfe.
- DR. WOLFE: Just following on Dr.
- Goldstein's comment, putting in the 15-minute you
- 13 have to wait in the office will make a huge
- 14 difference, because this puts a burden on the
- practitioner to make sure that someone doesn't walk
- out of the office, fall down, and get injured.
- 17 That's something that is very operative. If they
- don't tell the patient, the mother, as in what's now
- going to be in the VIS -- I mean, I assume that the
- VIS will be modified, in addition to just the
- labeling on that point. That is going to make a big
- difference. I don't think doctors, if they are aware

- of that -- and they should be aware of it with some
  mailing from the company -- are going to let someone
- walk out of the office. That will at least take care of the injuries from the syncope, if not the syncope.
- DR. NGUYEN: And FDA did co-author an MMWR with CDC, of which Andrea Southern is one of the main authors, who's sitting in the audience, that delved right into the VAERS data and explained the risk as
- 10 CHAIRMAN ROSENTHAL: Yes, Dr. Rakowsky.

well as the prevention strategy available.

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- DR. RAKOWSKY: As a person who works in a 11 general pediatric clinic in the residency program, we 12 did get communications both from the sponsor and FDA 13 about the 15 minutes. Actually, we block off a 15-14 minute block for that room afterwards. So I think 15 the communication was fairly clear. Ιt wasn't 16 mandated per se, but most people, at least in our 17 area, do block off that room afterwards, just because 18 of the communication that came from CDC and FDA. 19
- 20 CHAIRMAN ROSENTHAL: I love it when the 21 process is working.
- I understand that we're going to be talking

- about Gardasil again in about a year.
- 2 So shall we go to slide 30.
- 3 (Screen.)
- Slide 30 brings us to the question of whether our recommendation would be that the FDA continue its current safety monitoring, but also its current practices of keeping up with new information, as it seems to be doing so well. Are we ready for a vote? Ms. Celento.
- MS. CELENTO: Can I just confirm then that the self-controlled case series is considered part of the normal standard?
- DR. NGUYEN: Absolutely, absolutely.
- 14 CHAIRMAN ROSENTHAL: Then Dr. D'Angio.
- I think I'd make a more D'ANGIO: 15 general plea. When these questions come up, routine 16 safety monitoring can mean all sorts of different 17 things depending on the specific product. If there 18 are components to that routine safety monitoring 19 besides we'll wait until somebody tells us something 20 happens, it might be helpful to have that in the 21 question, because we tend to spend about 15 minutes -22

- there are times when we spend some time at this point deciding what the question is.
- DR. MURPHY: You're correct, and actually we had a sidebar discussion saying we should have done that for you on this one, because we do have in the review, we do have this follow-up study. It is important and we probably should have put it in the conclusion, so that you would know that that's part of the follow-up, because the slides do go up by themselves.
- Well, with CHAIRMAN ROSENTHAL: those 11 amendments, does the committee concur that the FDA 12 its safety monitoring with should continue 13 expansive definition of "safety monitoring," 14 include the studies that are ongoing and the plans 15 that have been articulated today? All in favor of 16 that? 17
- 18 (A show of hands.)
- 19 CHAIRMAN ROSENTHAL: Please keep your hands 20 up for a moment.
- 21 (Pause.)
- 22 CHAIRMAN ROSENTHAL: Any opposed?

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(No response.)
 1
                 CHAIRMAN ROSENTHAL: Any abstentions?
 2
                 (No response.)
 3
                 CHAIRMAN ROSENTHAL: I see none and none.
 4
                Dr. Towbin, can you get us started?
 5
                DR. TOWBIN: A robust yes.
 б
                DR. SHWAYDER: Tor Shwayder. I concur.
 7
                DR. D'ANGIO: Carl D'Angio, concur.
 8
                DR. MOTIL: Kathleen Motil, concur.
 9
                DR. RAKOWSKY: Alex Rakowsky, concur.
10
                DR. SANTANA: Victor Santana, agree.
11
                MS. CELENTO: Amy Celento, concur.
12
                DR. KRISCHER: Jeff Krischer, concur.
13
                DR. HOLMES: Greg Holmes, agree.
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                DR. NOTTERMAN: Notterman, agree.
15
                DR. WAGENER: Jeff Wagener, agree.
16
                DR. LA RUSSA: Phil La Russa, concur.
17
                DR. WOLFE: Sid Wolfe, agree.
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                CHAIRMAN ROSENTHAL: All right. Well, that
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       concludes our discussion of Gardasil. Thank you all
20
       very much. We appreciate your presentations and the
2.1
       informative discussion.
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2.2

- 1 Let's move ahead with a discussion -- we're
- a little ahead of schedule now -- for Xyzal. I hope
- 3 I'm pronouncing that correctly. Our presenter today
- will be Dr. Amy Taylor.
- Dr. Taylor attended medical school at Howard
- 6 University. She completed her pediatrics residency
- at Madigan Army Medical Center in Tacoma, Washington.
- She has a master of health science in health policy
- g from Johns Hopkins University and she's been on the
- 10 FDA team for the last four years.
- So, Dr. Taylor, thank you for presenting
- 12 Xyzal.
- 13 (Screen.)
- 14 XYZAL (LEVOCETIRIZINE DIHYDROCHLORIDE)
- DR. TAYLOR: Thank you. As was mentioned,
- today I'll present the safety review for Xyzal, or
- 17 levocetirizine.
- 18 (Screen.)
- This is an outline of the topics I will
- 20 cover today. You will see that I will present a
- 21 brief overview of the 2003 PAC presentation and the
- 22 2004 safety report on Cetirizine. This information

- is relevant because levocetirizine is the principal pharmacologically active component of Cetirizine.
- 3 (Screen.)
- forms There are two dosage for Xyzal 4 approved in the United States, a 5 milligram oral 5 tablet and a 2.5 milligram per 5 ml solution. Xyzal 6 is an H1 receptor antagonist which is marketed by 7 tablets are Incorporated. The originally UCB, 8 approved -- were originally approved for marketing on 9 May 25, 2007, and the solution was approved for 10 marketing on January 28, 2008. 11
- Pediatric exclusivity was granted on August 25, 2009, and the trigger for this review, PREA and BPCA labeling changes, occurred on August 21, 2009.
- 15 (Screen.)
- 16 Xyzal is indicated in adults and pediatric
  17 patients for the relief of symptoms associated with
  18 seasonal allergic rhinitis in patients two years of
  19 age and older and perennial allergic rhinitis in
  20 patients six months of age and older.
- It's also indicated in the treatment of  $^{22}$  uncomplicated skin manifestations of chronic

idiopathic urticaria in patients six months to five 1 years -- sorry. Six months and older. I'm sorry.

(Screen.) 3

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The dosing is broken down by age, with dosing for adolescents and -- adults and children 12 years and older, for children 6 to 11 years, and children 6 months to 5 years.

(Screen.)

Over a period of three years from August 9 2007 to July of 2010, there were over 5.5 million 10 prescriptions, of which 15 percent were pediatric 11 The past year, from August 2009 to prescriptions. 12 July 2010, saw increase of 1.2 an million 13 prescriptions, of which 17 percent were pediatric 14 Almost 80 percent of prescriptions. pediatric 15 prescriptions were to patients 6 years to 16 years. 16

> Prior to issuing a written request for Xyzal, clinical trials were conducted in children and adolescents ages six and older. Adolescents age 12 and older were studied with adults in the original clinical trial submitted for approval.

(Screen.) 22

There were three pediatric studies conducted under a written request: a retrospective population pharmacokinetic study in patients one to five years, and two randomized, placebo-controlled, two-week safety trials, the first in patients 6 to less than 12 months and the second one in 1 to 6 year olds.

7 (Screen.)

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Efficacy for allergic rhinitis and chronic idiopathic urticaria in pediatric patients was extrapolated from evidence in adult patients and supported by pharmacokinetic and safety studies in children.

13 (Screen.)

This slide shows the safety results from the exclusivity studies.

16 (Screen.)

The next few slides review the current safety labeling. You'll see here that we have the contraindications and the warnings and precautions section.

21 (Screen.)

Adverse reactions in greater than or equal

- 1 to 2 percent of patients are presented in tabular
- form by age. First is adults and adolescents 12
- years and older.
- (Screen.)
- 5 The next one is patients 6 years to 12
- 6 years.
- 7 (Screen.)
- One to five years.
- g (Screen.)
- And then patients 6 to 11 months, adverse
- 11 reactions were reported -- adverse reactions which
- were reported in more than one patient, or greater
- than or equal to 3 percent of patients, and were also
- more common with Xyzal than placebo, are presented in
- labeling in text form.
- 16 (Screen.)
- There's also information on post-marketing
- 18 experience in the labeling.
- 19 (Screen.)
- Now I want to turn our attention to the
- adverse events reports since marketing approval. You
- can see from this chart that there were 38 crude

count pediatric AERS reports, all serious, and no deaths.

3 (Screen.)

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30 pediatric -- 38 reports in pediatric patients were found with the initial search. Ten additional pediatric reports were found in reports with null age. This includes six fetal exposure cases. After one duplicate report was removed, a total of 47 non-duplicated reports were reviewed.

(Screen.)

There were six fetal exposures reported 11 since marketing approval. Two had an outcome of 12 therapeutic abortions and one had an outcome of a 13 spontaneous abortion. The other three fetal 14 exposures had an outcome of prematurity, fetal growth 15 retardation, and meconium-tinted amniotic fluid and 16 otherwise healthy infants. 17

(Screen.)

There were 12 cases in which an incorrect dose administration or a drug dispensing error occurred. Seven of these cases and one additional case which did not mention a medication error

involved a concentrated drop formulation which is not approved in the U.S.

3 (Screen.)

There were five medication error cases involving the tablet or liquid formulation, which is approved in the U.S. Three involved accidental ingestions and there was one case each involving dispensing error and administration error.

g (Screen.)

In the next two slides I have listed the number of serious adverse events by system organ class. I've excluded the 6 fetal exposure cases and the 13 medication errors, leaving 28 cases. Most of the cases reported more than one adverse event, which is why the numbers do not add up to 28.

16 (Screen.)

17 This just continues that chart.

18 (Screen.)

Nervous systems adverse events included somnolence, syncope, and dizziness.

(Screen.)

There were 13 general disorders and

- administration site conditions, including fatigue,
- pain, and asthenia.
- 3 (Screen.)
- There were 13 psychiatric disorder adverse
- 5 events reported, including suicide attempt and
- 6 ideation.
- 7 (Screen.)
- Now I want to take a break from my
- 9 presentation of levocetirizine adverse events to
- 10 discuss safety information related to Cetirizine
- 11 which has been presented in the past. As mentioned
- 12 previously, levocetirizine is the principal
- pharmacologically active component of Cetirizine.
- In 2003 the safety review of Cetirizine was
- presented to the PAC. In addition, FDA conducted a
- 16 review of suicidality adverse events associated with
- 17 Cetirizine in 2004.
- 18 (Screen.)
- In 2003 the safety review for the PAC found
- 20 that about one-fifth of reports were medication
- errors, due primarily to confusion between Zantac and
- 22 Zyrtec; one-fifth of reports were psychiatric events;

and one-fifth were neurological events. The rest were scattered among other system organ classes.

3 (Screen.)

Also in 2003, information about a review which had been conducted in 2001 which suggested a probable linkage between the use of Cetirizine and the incidence of hallucinations was presented. There were two reported cases of hallucinations in pediatric patients during the one-year postexclusivity period for Cetirizine.

11 (Screen.)

Now I'm going to switch gears a little bit more and discuss suicide-related events associated with Cetirizine. In 2004, FDA reviewed adult cases of suicide-related events and acute intentional overdose associated with Cetirizine.

In eight cases the patient was taking Cetirizine before the event and there was no apparent alternative explanation for the event. The conclusion was that Cetirizine may be associated with suicide-related events in some patients.

22 (Screen.)

Now let's take a look at pediatric suiciderelated events with Xyzal, or levocetirizine. Of note, the majority of cases -- in the majority of cases, the patients were not taking Xyzal prior to suicide attempt or ideation.

Four cases are presented in the next two slides in which Xyzal was intentionally ingested in a suicide attempt. The patients were not taking Xyzal prior to the event. You see the 13 year old female and the 14 year old female here.

(Screen.)

As well as a 14 year and 16 year old on the next slide. The last case on this slide is of a 15 year old who was on Xyzal for four days. He became agitated and fearful at night. He then became weepy, depressed, and had suicidal thoughts. The patient recovered with discontinuation of Xyzal.

(Screen.)

Based on the adverse events seen in Cetirizine of hallucination and suicide ideation, these have been included in Xyzal labeling since marketing approval in May of 2007. You can see the

post-marketing experience information here from the labeling.

3 (Screen.)

2.2

I will now continue with the presentation of adverse events reported with levocetirizine. There were two cases of Stevens-Johnson Syndrome reported.

7 (Screen.)

The first case involves a 12 year old male who developed a bright red area on his abdomen. The patient was diagnosed with shingles and cellulitis and was treated with Bactrim and acyclovir. The affected area worsened and a biopsy was consistent with erythema multiforme or Stevens-Johnson Syndrome.

Of note, Bactrim and acyclovir are labeled for Stevens-Johnson Syndrome. Xyzal is not.

The second case involves a 16 year old male with facial edema four days after starting Xyzal. The patient was diagnosed with Stevens-Johnson Syndrome. No biopsy information was available in the report. Concomitant medications include Rovamycin, which is not approved in the United States. And the patient improved.

1 (Screen.)

A look at AERS reports in adults found one 2 of Stevens-Johnson Syndrome/Toxic Epidermal case 3 Necrolysis, two cases of TEN, and one case of toxic 4 These cases are complicated by the skin eruption. 5 presence of multiple medications, lack of biopsy 6 confirmation, and two questionable reports indicating 7 rash appeared following discontinuation 8 levocetirizine. 9

10 (Screen.)

The next two slides list the other serious adverse events by system organ classes.

13 (Screen.)

14 (Screen.)

In summary, no safety issues unique to the 15 identified. pediatric population were The 16 contributory role of levocetirizine in Stevens-17 Johnson Syndrome is unknown, and the use of Xyzal is 18 accounting increasing, with pediatric use for 19 approximately 17 percent of all prescriptions. 20

(Screen.)

The FDA will continue its standard ongoing

- safety monitoring for Xyzal. Does the advisory committee concur?
- 3 (Screen.)
- I'd like to thank the following people for their help with this presentation, in particular Melinda Wilson and Anthony Durmowicz.
- 7 CHAIRMAN ROSENTHAL: Thank you, Dr. Taylor. 8 That was a very nice presentation.
- of -- on slide 8 there were two safety trials that
  were described, one with an N of 45 and the other
  with an N of 114. My question is how does the agency
  decide how to -- how to power these studies, what
  sample sizes should be used for safety events?

It seems to me that these types of samples 15 sizes really would only be powered sufficiently to 16 identify very prevalent adverse events and ones for 17 which there were pretty grand disparities between the 18 two groups. So really that's just a general question 19 about how does the agency approach this issue of 20 studying safety end points, as opposed to efficacy 21 end points. 22

- DR. MURPHY: I'll take a shot, Ann, and then
- 2 you.
- We don't power them for safety usually. In
- a normal safety and efficacy trial, it's powered for
- 5 the efficacy, and then you describe the safety. And
- if you have a signal, then you would have a post-
- 7 marketing requirement potentially for additional,
- g unless you go into the trial knowing beforehand from
- g some other data that you have something you want to
- try to better understand as far as the safety.
- But in the routine practice, you're not
- powering the trial for safety.
- 13 CHAIRMAN ROSENTHAL: So that was my
- understanding before I looked at slide 8 as well.
- But slide 8, the second two bullets each describe
- these as being placebo-controlled, two-week safety
- 17 studies. So that's why I asked the question. Maybe
- this is emphasizing an element of what was hoped for
- 19 from these studies that was other than the primary
- 20 end points of efficacy.
- DR. TONY DURMOWICZ: Can I address it a
- 22 little bit?

- 1 CHAIRMAN ROSENTHAL: Yes, please do.
- DR. MURPHY: Would the division please
- introduce yourselves. We didn't do that. Please
- introduce yourself, please.
- 5 CHAIRMAN ROSENTHAL: Your mike is not on.
- DR. TONY DURMOWICZ: I'm Tony Durmowicz.
- 7 I'm one of the medical officer team leaders in the
- 8 Division of Pulmonary Allergy and Rheumatology.
- Just to kind of add on to what Dianne was
- saying, each drug is considered somewhat individually
- when you consider how much safety data do you need,
- and there are ICH guidelines for chronic indications
- 13 and less than chronic indications on how many
- patients should be studied and a general concept for
- how long.
- Now, with regard to Xyzal or levocetirizine
- in pediatrics, several things come into play. One is
- what Amy had already mentioned, that it is basically
- the same active drug as Zyrtec, which had been on the
- 20 market for a long time and given to children and is
- now over the counter.
- The other aspect was in the original

which wasn't part of this submission, advisory 1 committee review, there was a pediatric study in 2 children 18 months to 24 months of age where they 3 took levocetirizine for 18 months continually at a twice-daily level, that was probably a little higher 5 dose than what we approve for in general. 6 into context with regard to the pediatric 7 requirements, the studies in specific populations 8 with the very young children, because they weren't 9 included in that other population, and children who 10 had specific SAR and PAR were deemed necessary for 11 the pediatric age group. 12

So like I said, everything is taken into what you know already about each individual product, and that's what came up with this. A lot of the information regarding the young children and those two-week studies that were done, part of the non-efficacy aspect of it or safety aspect of it, if you will, in a broader sense was to assess the pharmacokinetics, to get a good pharmacokinetic link between the adult data.

So that's kind of like the long answer.

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- 1 CHAIRMAN ROSENTHAL: That's very helpful.
- 2 Thank you.
- 3 DR. MURPHY: I was going to add on that what
- 4 you'll see sometimes in the pediatric studies is
- 5 that, particularly where they're extrapolating
- efficacy, unless again there's a signal that they
- yant -- and again, you heard, they had all this other
- background information, so they want to have another
- g study.
- It's labeled safety, but we're trying to
- tell you the only safety data we had was out of these
- basically pharmacokinetic studies.
- 13 CHAIRMAN ROSENTHAL: Okay, thank you.
- 14 Yes, Dr. Santana.
- DR. SANTANA: This is more of a historical
- 16 question. So I was puzzled why in the dosage
- 17 information for children six months to five years
- there was a fixed dose, which you know really
- encompasses a wide range of weights and body surface
- areas within that age group. So how does the agency
- 21 -- maybe you could give me a general answer. How
- does the agency approach some of these symptom relief

- medications in terms of dosage parameters?
- 2 I'm used to dosing things on a milligram per
- kilo, milligram per surface area. But I'm an
- oncologist, I'll admit to that. But we don't use
- fixed doses. So I was surprised that, particularly
- in that age group, it was a fixed dose across a broad
- 7 range of patient weights and surface areas.
- DR. TONY DURMOWICZ: The dose of Xyzal and
- 9 levocetirizine has been dosed in different clinical
- trials, both on a milligram per kilo basis, which I
- just alluded to, as well as a fixed dosage schema, if
- 12 you will.
- 13 I think that the general answer to your
- question is that the individual sponsor will propose
- the dosing regimen, whether they want to do it on a
- 16 milligram per kilo or in a fixed dose regimen. When
- we take a look at that, both from a pharmacokinetic
- and a safety and an efficacy standpoint, we make a
- determination whether that PK variability between,
- like you said, a very large maybe differential in
- weights is acceptable or not.
- In this case, I think we apparently did. So

- I think that's the general answer. I don't have
- anything other --
- DR. SANTANA: An answer I've always heard is
- because there is no formulation that would apply to
- 5 kids and therefore you can't dose it in a broad
- for range. But in this case there is a formulation.
- 7 DR. TAYLOR: There is a formula.
- DR. MURPHY: I think the only answer that we
- g can give at this point is that pharmacokinetically
- 10 they looked at it and felt that that would be the
- best approach. If you have somebody who has a better
- answer, please provide it.
- DR. RAY: I'm Partha Ray. I'm the original
- 14 clin-pharm reviewer of Xyzal. The other thing that
- is in the equation both I think Cetirizine and Xyzal
- 16 -- for Cetirizine, I now that 10 and 5 milligram,
- both doses were quite effective. So the efficacy is
- very broad in the range of doses. So if you go back
- to the Xyzal, you have that.
- So we felt when we looked at the PK data,
- the six months to one year kids probably was showing
- a little bit less exposure if you dose following the

- label, but we felt comfortable that that's the most vulnerable population and the efficacy will still be there and the exposure would be slightly lower than the adults on an average. Again, there were of course individual variations, but we thought from a safety point of view that the exposure -- we want to keep it below the adults and also maintain the efficacy.
- 9 So that was sort of the approach we took.
- DR. MURPHY: I guess his question, though, 10 was against the entire age range and weight range of 11 five years, you thought the six months to 12 milligrams gave the same exposure whether you were 13 dealing with a small six month old, who was going to 14 get a higher dose, and the five year old, who was 15 going to get a lower dose; that it still was in the 16 efficacy range noted in adults. So instead of having 17 different doses, they did it that way. Is that 18 correct? 19
- DR. RAY: Yes, that's true.
- 21 CHAIRMAN ROSENTHAL: Dr. Shwayder.
- DR. SHWAYDER: I guess two questions.

First, it seems to me -- correct me if I'm wrong -that the company came up with a levorotatory salt two
because its patent was running out on the first one
and they just wanted to extend its exclusivity for
something that's over the counter. And was there a
huge amount of difference in the side effects from
Cetirizine to the levocetirizine? I'd imagine not.

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I guess my next question is how do you break off what they're calling side effects, but would in fact be reasons why you are giving the medicine, for example urticaria or pruritus or rash like eczema? I see my allergist colleagues give Xyzal for atopic dermatitis fairly frequently. Is there a way in the mining of the data to say, oh heavens, that's not a side effect; that's just why you gave the medicine in the first place.

DR. McMAHON: The answer as far as the first question is concerned, whether there's a different adverse event pattern I guess with the generic, from the point of view of AERS it's very, very difficult to determine that. I'm not sure if you've looked at that; have you, Melinda?

- DR. MELINDA WILSON: I'm Melinda Wilson.
- 2 I'm a safety evaluator in the Division of
- 3 Pharmacovigilance. I can say from reviewing the
- report that Dr. McMahon refers to that in some cases
- 5 patients were receiving levocetirizine for the
- 6 treatment of urticaria or hypersensitivity and the
- 7 reports would suggest that the hypersensitivity
- g syndrome or the urticaria continued to get worse
- despite treatment, and in some ways that's considered
- an adverse event due to lack of effect.
- But I do concur with your original opinion
- that it is difficult to sort of separate the weeds,
- if you will, in those cases.
- DR. SHWAYDER: Thank you.
- DR. MURPHY: We do have a category called
- 16 "lack of effect." Sometimes they would put that in
- that category, but they may not.
- DR. SHWAYDER: Yes, I noted that with
- 19 Ulesfia, lack of effect.
- DR. McMAHON: As far as the question about
- looking actually for adverse events that are perhaps
- associated with the indication versus, say, adverse

- events from the medicine, that is something that we
- 2 routinely look for when we're evaluating our, say,
- data mining runs or when we're just looking at crude
- d count data, because it's quite easy to pick out the
- 5 confounding by indication. It's something that we do
- 6 routinely.
- You can't always be 100 percent sure. There
- are situations where events that are associated with
- g the indication can be worsened by the drug. That
- does happen, but it's not all that common. So we
- definitely look for that.
- 12 CHAIRMAN ROSENTHAL: Dr. Notterman.
- DR. NOTTERMAN: I have two questions. One,
- 14 with respect to the pharmacokinetics related to the
- parent compound: Is the exposure to the active
- 16 compound for levocetirizine given as levocetirizine
- about the same in terms of area under the curve as
- the exposure to levocetirizine when the parent
- 19 compound is given?
- DR. RAY: Yes, that is correct.
- DR. NOTTERMAN: So that's probably how these
- doses were --

- DR. RAY: Yes.
- DR. NOTTERMAN: Secondly, with respect to
- suicide, which appears in the signal with respect to
- both drugs -- and I thought I saw one reasonably
- 5 convincing case of suicidal ideation that began after
- the drug was started.
- 7 CHAIRMAN ROSENTHAL: Yes, case number five,
- g right.
- DR. NOTTERMAN: And receded when it was
- 10 stopped. So that seemed to be a significant signal.
- I wondered how prominently you decided to feature
- suicidal ideation in the label. In the case of other
- drugs we've looked at, it's prominently figured.
- Here it seems to just be listed as part of a longer
- sentence or a list of symptoms. I wondered if you
- could comment on that, somebody from the division can
- 17 comment on that?
- DR. TONY DURMOWICZ: Right now the suicidal
- ideation listing on the label is under post-marketing
- with a reference to Cetirizine, to Zyrtec, because it
- was seen in the Zyrtec profile, even though it is the
- same drug. That's why it was linked together in the

- 1 Xyzal label.
- $_{\rm 2}$   $\,$  This is the first AERS report I think we
- 3 have of somebody who has suicidal thoughts or
- ideation and weeping, if you will, taking Xyzal.
- DR. NOTTERMAN: So do I take from that that
- gou don't think, given what you know about this drug
- and the parent compound, that suicidal ideation might
- be better if it were more prominently featured? It's
- buried in a fairly long sentence here.
- DR. TONY DURMOWICZ: I think -- and this is
- my interpretation, not the division's. That will
- always get you in trouble sometimes. But the concept
- would be to put suicidal ideation under the Xyzal
- label and not refer to Cetirizine, even though
- they're the same drug. Personally, one out of, I
- don't know, 5 million prescriptions or whatever, I'm
- not sure it goes into the warnings and precautions
- section. That could be a debatable thing. You've
- got one case out of all this and the history with
- 20 Cetirizine itself. So that's a judgment call.
- DR. MELINDA WILSON: If I could just add a
- few comments regarding the case of the suicidal

- ideation. This case both Dr. Taylor and I discussed 1 and agreed that it was somewhat challenging 2. evaluate because all of the information provided in 3 the case came from the mother and included a good subjective language. And although the degree of 5 event did appear to occur and we certainly do 6 appreciate the information she provides, it's 7 difficult to evaluate the contribution of 8 concomitant medications, an existing family 9 situation. She mentioned that they recently moved 10 and that there could be some other issues ongoing in 11 the case. 12
- So having said that, it was challenging.
- DR. NOTTERMAN: Just one follow-up, if I
- 15 may.
- 16 CHAIRMAN ROSENTHAL: Please.
- DR. NOTTERMAN: I appreciate 17 difficulty, and of course -- I wonder, however, if 18 is a way of continuing to monitor 19 possibility or the frequency of suicidal ideation 20 with this pair of drugs that is a little bit more 2.1 intensive or likely to detect a signal than returning 22

- routine monitoring with respect to to that 1 particular evolution. 2.
- MELINDA WILSON: Certainly that's a DR. 3 possibility. One thing that I did want to comment on is that Dr. McMahon and I did discuss data mining 5 analysis to evaluate the disproportionate reporting 6 of suicidal events with levocetirizine versus other 7 antihistamines, and in comparison, say, for example 8 did to Cetirizine there not appear to 9 disproportionate reporting with levocetirizine. But 10 certainly we will continue our ongoing monitoring.
- CHAIRMAN ROSENTHAL: Yes, Dr. Farrar. 12

- DR. FARRAR: Have there been reports with 13 other antihistamines, like Loradidine, or are you 14 able to discuss that? 15
- I don't know -- I don't DR. TONY DURMOWICZ: 16 have any concept of any individual antihistamine. 17 But I think in general, in the allergic rhinitis 18 population, SAR, PAR, their suicidal type tendencies 19 are higher than the general population. So that's 20 somewhat of a little bit of a confounding thing. 21
- I don't know in particular if any other 22

- antihistamines have suicidal issues. I know there's
- an ongoing suicidal issue with Cingulair, which has
- continued to be evaluated, that you may know.
- 4 CHAIRMAN ROSENTHAL: Am I missing any latent
- 5 questions?
- 6 (No response.)
- 7 So the question before us is whether or not
- 8 the agency should continue standard ongoing safety
- 9 monitoring and included in that, Dr. Notterman, I'm
- 10 sure is continued focused look at suicide-related
- outcomes. So does the committee concur that the
- agency should continue this strategy? All in favor?
- (A show of hands.)
- 14 CHAIRMAN ROSENTHAL: Any opposition?
- 15 (No response.)
- 16 CHAIRMAN ROSENTHAL: Any abstentions?
- 17 (No response.)
- CHAIRMAN ROSENTHAL: Dr. Towbin, will you
- 19 get us started again?
- DR. TOWBIN: I concur and also appreciate
- the attention to the psychiatric issues with this
- agent and Cetirizine.

- DR. SHWAYDER: Tor Shwayder. I concur.
- DR. D'ANGIO: Carl D'Angio, concur.
- DR. MOTIL: Kathleen Motil, concur.
- DR. RAKOWSKY: Alex Rakowsky, concur.
- DR. SANTANA: Victor Santana, agree.
- MS. CELENTO: Amy Celento, concur.
- 7 DR. KRISCHER: Jeff Krischer, concur.
- DR. HOLMES: Greg Holmes, concur.
- DR. NOTTERMAN: Daniel Notterman, concur,
- and I would like to stress that I think it's
- important to continue to have ongoing monitoring for
- 12 psychiatric complications, not just suicidal
- ideation, but others as well.
- DR. WAGENER: Jeff Wagener, agree.
- DR. LA RUSSA: Phil La Russa, concur.
- DR. WOLFE: Sid Wolfe, concur.
- 17 CHAIRMAN ROSENTHAL: All right. Thank you
- all very much.
- 19 It's time now to break for lunch. I'd ask
- that everyone -- first, before people ditch the room,
- 21 please honor our tradition and our expectation that
- we won't discuss the matters of the meeting, the

1	matters before the committee, in contexts away from
2	this table, including in the lunch room and other
3	places.
4	We need to return promptly at 1:00 because
5	we've got the public, open public forum, and we need
6	to be on time for that. So thank you all very much.
7	Enjoy your lunch and I'll see you at 1:00.
8	(Whereupon, at 11:53 a.m., the meeting was
9	recessed, to reconvene the same day.)
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CHAIRMAN ROSENTHAL: By my clock it's 1:00 3 o'clock. While people are finding their seats, let me just make a quick announcement that Theresa Allia, 5 who is outside, who has been helping us so much 6 around the coordination of these meetings these last 7 few days, will also help you with arrangements 8 related to transportation to and from, or to the 9 airport. So if you haven't already, if you need a 10 cab, speak with Theresa during the next break. 11

## 12 OPEN PUBLIC HEARING

13 CHAIRMAN ROSENTHAL: And now it's time

14 for the open public forum. We'll start this by a

15 statement that I'll read.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, 1 open public hearing speaker, at the beginning of your 2. written or oral statement to advise the committee of 3 any financial relationship that you may have with the sponsor, its product, and its direct competitors.

- For example, this financial information may б include sponsor's payment of your the travel, 7 lodging, or other expenses in connection with your 8 attendance at the meeting. 9
- Likewise, FDA encourages you the at 10 beginning of your statement to advise the committee 11 if you do not have any such relationships. 12 choose not to address this issue of financial 13 relationships at the beginning of your statement, it 14 will not preclude you from speaking. 15
- With that, I'd like to open the open public 16 hearing part of our meeting. I have that Dr. Dianne 17 Zuckerman, who is the President of the National 18 Research Center for Women and Families, will be 19 speaking. 20
- MS. DE BRAVO: Dr. Zuckerman couldn't be 2.1 here today, so I'm going to speak in her stead. 22

- Brandel France de Bravo and I'm pleased to have the opportunity to speak on behalf of the National Research Center for Women and Families and our Cancer Prevention and Treatment Fund, albeit an hour and a half after the conclusion of the discussion of Gardasil, which is the subject of my comments.
- Guillain-Barre Syndrome is one of the conditions of special interest -- oh, and by the way, our center doesn't accept contributions for companies that make medical products and so we have no conflict of interest.
- Guillain-Barre Syndrome is one οf the 12 conditions of special interest you heard about and 13 being closely monitored among individuals 14 vaccinated with Gardasil. In the general population, 15 GBS has a average weekly incidence of 0.65 to 2.5 16 cases per week per 10 million people. As those 17 condition numbers indicate, this sometimes fatal 18 causing temporary and even permanent paralysis is, 19 thankfully, exceedingly rare. It is, however, one of 20 the known neurological sequelae of vaccination. 2.1

The question is, is GBS more prevalent among

people receiving Gardasil. In a new study to be 1 published in Vaccine, Nazar Sowaya and coauthors 2. looked at the VAERS database between June 2006 and 3 September 2009 and compared the occurrence of 4 after vaccination with Gardasil to the occurrence 5 after vaccination with Menectra and influenza. 6 researchers concluded that the average weekly 7 reporting rate of GBS for the six weeks 8 vaccination was 6.6 events per week per 10 million 9 subjects, which is double what it was for Menectra 10 and about five times the weekly reporting rate for 11 flu vaccine. 12

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Now, three CDC researchers in their comment or their letter following this have very appropriately pointed out that the VAERS database has numerous shortcomings and that the authors used as their denominator the number of doses distributed divided by three, even though we all know not everyone receives all three doses. They also maintain that, being a new vaccine, adverse reactions to Gardasil were overreported.

We disagree. While the authors may have

2 also worked with too small a numerator. Because 3 VAERS is a passive system that depends on voluntary

worked with too small a denominator, we believe they

- 4 reporting, adverse reactions are always
- underreported. Most parents don't know how to report
- 6 problems or don't find the time to do so, and many
- doctors underreport as well.

- Should we be concerned about the safety of 8 Gardasil? All of us are here today because we care 9 about the safety of pediatric medications and 10 Moreover, as public health professionals vaccines. 11 we all recognize that a certain amount of individual 12 risk is absolutely acceptable for the public good. 13
- This is why we can't talk about Gardasil safety without discussing its efficacy. We must ask, what level of protection does it offer and for exactly how long. We must weigh the vaccine's risks and costs against its benefits, knowing that the balance sheet will look different in each country and even in different communities.
- Gardasil's use continues to expand in the U.S. even though cervical cancer screening is

- affordable and widely available and penile cancer and
- vulvar cancer, for instance, are extremely rare.
- 3 Here in the U.S., Gardasil's main benefit is a
- $_{\it d}$  reduction in abnormal pap tests and excisional
- 5 therapies for CIN-2 and 3 lesions. Will Gardasil
- 6 prevent cervical cancer? We still don't have the
- 7 long-term data to determine that.
- 8 Similarly, we don't know how long this
- yaccine, one of the most expensive vaccines and the
- 10 most expensive routine vaccination ever, how long it
- 11 lasts.
- 12 Without that information, vaccinated girls
- and women, as well as boys and men, could become
- 14 complacent and fail to take proper precautions.
- Modeling analysis done by Rouan Barnabas shows that a
- 16 cervical cancer vaccine must last at least 15 years
- in order to prevent cancer and not just postpone it.
- According to the data we have on Gardasil so far,
- 19 its protection is expected to last at least five
- years. But unless it lasts significantly longer, we
- 21 may find that girls and boys vaccinated as preteens
- are losing their immunity when they are most sexually

active. 1

Menectra.

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- Ιf we find out that booster shots 2 needed, will young adults who were vaccinated 3 children actually get them? What if the booster is 4 expensive and they don't have coverage for it?
- Now, although Gardasil is safe for most б people, Sowaya's study found that girls and young 7 women vaccinated with Gardasil were 8.5 times more 8 likely to visit the ER, 12.5 times more likely to be 9 hospitalized, 10 times more likely to have a life-10 threatening event, and 26.5 times more likely to have 11 a disability, than young people vaccinated with 12
- Those numbers would be acceptable if 14 Gardasil saves lives. But we don't yet know if it 15 will. 16
- In summary, the FDA approved Gardasil on the 17 basis of short-term research and we don't yet know 18 how long Gardasil provides protection or when a 19 booster shot will be needed. We also don't know 20 whether vaccinated girls will grow up to be women who 21 are less likely to undergo pap smears for HPV testing 22

- because they think they are guaranteed to be one less
- $_{\rm 2}$   $\,$  woman with cervical cancer, as the ad campaign had
- 3 promised.
- There are a lot of unanswered questions and
- 5 we hope you'll recommend that the FDA regularly
- 6 reevaluate Gardasil's use as new research data on
- safety and efficacy become available, which is what
- g you did today.
- 9 So thank you very much for allowing me to
- 10 comment.
- 11 CHAIRMAN ROSENTHAL: Thank you for your
- 12 comment.
- 13 We received one comment electronically and
- 14 I'll just read the parts of that that seem related to
- the topic of discussion today. It's from Gene Public
- and the bulk of the communication is on the subject
- line of an email. The text of the email, the body of
- the email, I won't read because the comments are not
- 19 relevant.
- From the subject line, it says: "Terrible"
- 21 -- and I'm going to apologize because it's not
- 22 punctuated in a way that makes it easy to read, but

- bear with me. "Terrible level of carelessness by
- 2 pediatric practitioners. The focus on making money
- from approving new vaccines by big pharma profiteers
- $_{oldsymbol{arphi}}$  is beyond belief, hurting America, and it is well
- beyond public safety standards. Gardasil has killed
- some kids and injured others. In addition, the
- agency pays zero attention to epigenetics and the
- effect on future generations of drugs that are taken.
- g It is time to require that all big pharma execs that
- 10 come to you for drug approval need to testify that
- they and their families have taken the drug four
- years ago and are still living."
- 13 That's the end of anything that I would say
- is related to the topic of drug safety.
- DR. MURPHY: Walt, we do have posted some
- other comments, don't we?
- DR. ELLENBERG: Not for Gardasil.
- DR. MURPHY: Not for Gardasil? Okay. Thank
- 19 you. Just wanted to make sure.
- 20 CHAIRMAN ROSENTHAL: There are no other
- 21 comments. So that's going to conclude the open
- public forum, and we'll move up the presentation on

- 1 Flovent HFA. Dr. Notterman, if you can recuse 2 yourself we'd appreciate that.
- Dr. Virginia Elgin will be presenting the safety review information for Flovent. Dr. Elgin is a board-certified pediatric neurologist who did her pediatric internship and residency at Boston City Hospital and Inova Fairfax Hospital. She completed an adult neurology residency and a child neurology fellowship at Columbia Presbyterian Hospital.
- Dr. Elgin saw child neurology patients for 10 years working for Mercy Hospital several in 11 Pittsburgh, Pennsylvania, and then Inova Hospital in 12 Fairfax. She's been with the FDA for four and a half 13 years as a medical officer, working primarily in the 14 drugs used to treat inborn errors of 15 metabolism. 16
- Dr. Elgin, thank you for coming to present to us today.
- 19 (Screen.)
- 20 FLOVENT HFA
- DR. ELGIN: Thank you for allowing me to present. Welcome, everybody. I've got to warn you

- in advance, I've got a little bit of a tremor in my
- hands, but I did not have too much caffeine, so just
- bear with me if I have a little bit of a shaky hand.
- Today I'm presenting a focused safety review
- on Flovent to you.
- 6 (Screen.)
- 7 We'll be following this basic format, the
- same as the others.
- g (Screen.)
- 10 The original market approval for Flovent,
- otherwise known as fluticasone propionate, was May
- 14, 2004, for the adults and also children who are at
- least 12 years of age. There was a deferral on
- studies in children 6 to 11. That became a post-
- 15 marketing commitment -- requirement, rather, not
- 16 commitment. There was approval of extended age range
- in pediatrics down to four years, and that occurred
- in February of 2006.
- There was a written request issued initially
- 20 in 1999, June 1999, and amended in 2001. Pediatric
- exclusivity was granted February 25, 2003.
- (Screen.)

indications The current now include 1 maintenance treatment of asthma as prophylactic 2. therapy in patients four years of age and older. 3 is now also indicated for patients requiring oral 4 corticosteroid therapy of asthma. Many of these 5 people can reduce or eliminate the need for oral 6 corticosteroids over time with the use of Flovent. 7

(Screen.)

Flovent is fluticasone propionate. It comes
in three strengths, 44, 110, and 220 micrograms. It
is a corticosteroid inhalation aerosol. The sponsor
is -- okay, here we go -- GlaxoSmithKline. Got it.

13 (Screen.)

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There are a number of studies that have been done on Flovent in adults or adolescents 12 years of age or older. There was one study which was done -- let's see if I've got this pointer working here. Is this doing what I want it to do? Hold on.

Well, anyways, I'm just going to keep talking. Study 1 was on patients who were not well controlled on bronchodilators. You can see they used three different doses against placebo; improved

- asthma control was observed.
- 2 Study 2, patients not controlled on inhaled
- 3 corticosteroids. It was a 12-week study. Again,
- three different doses against placebo. Double-blind,
- placebo-controlled study; improved asthma control.
- Study 3, these people were on prednisone and
- this was a 16-week study and they used two different
- doses, 440 and 880, compared to placebo. What they
- g found was that patients taking Flovent require just
- about a third of the amount of prednisone that the
- 11 placebo required.
- 12 Study 4, patients taking high to low doses
- of inhaled corticosteroids, as well as other asthma
- 14 medications. This was a long-term safety study.
- Both the 220 and the 440 doses were found to be safe.
- 16 Study 5, patients taking moderate to high
- doses of inhaled corticosteroids. They were
- 18 comparing two different types of propellants.
- 19 Currently the only one approved is the HFA or
- 20 hydrofluoralkane propellant. The chlorofluorocarbon
- 21 propellant -- both of them were well tolerated.
- (Screen.)

- move to the 4 to 11 Now we year old 1 population. They had a 12-week study. This was an 2. interesting study in my mind, comparing 88 micrograms 3 BID to placebo, double-blind, parallel group. They had a significant improvement in their asthma, but 5 the weird thing about this study is that 13 percent 6 the placebo patients ended up with detectable 7 serum levels of Flovent. And therefore efficacy was 8 extrapolated from adult data. 9
- There was another study comparing the two propellants and they found that the overall exposure with HFA was -- Does this pointer work? Can anybody see it?
- I don't know. I can talk. I can talk; you can look.
- So that study was comparing the two propellants and they found out there was overall less systemic exposure.
- Thank you very much. All right. Well, you always feel better when you have a pointer, but it's not always necessary.
- Then there was a study done which was a one-

- day study, just seeing whether it made any difference
- 2 in systemic exposure having a face mask and a valved
- holding chamber, which of course it did.
- There was another study which looked at the
- bypothalamic pituitary adrenal axis study, and what
- 6 they found in this four-week study was that the
- 7 safety profile was similar to adults.
- Finally, again, this last study actually
- yent up to 16 years of age, comparing 88 micrograms
- in both of these different propellants, and they were
- found to be safety profiled similar.
- 12 (Screen.)
- In the patient population less than four
- years, there was a 12 week study done which showed a
- difference between placebo and the patients getting
- 16 Flovent at a greater frequency of 3 percent with
- pyrexia, nasopharyngitis, upper respiratory tract
- infections, vomiting, otitis media, bronchitis,
- pharyngitis and viral infections.
- Again, another study showing higher exposure
- 21 with Aerochamber.
- There was a 52-week study looking at linear

- growth and asthma symptoms, comparing Flovent to
- 2 Cromolyn. In that study there was a trend favoring
- asthma symptoms in Flovent. That was 2.5 centimeters
- or less growth with the Flovent.
- A four-week PK study was done, showing a
- slight decrease in serum cortisol.
- 7 (Screen.)
- 8 So all of this led to some labeling updates.
- 9 In February, 2006, PK and PD and safety data in
- patients 4 to 11 years of age was included, including
- information about 56 patients 4 to 11 who took 88
- micrograms twice a day for 4 weeks and adverse events
- were noted to be similar to those in adults.
- 14 Information on pediatric trials which
- included extrapolation of efficacy in the 4 to 11
- year old age range was included. And they also
- included information comparing the two different
- propellants and the use of the Aerochamber.
- 19 (Screen.)
- July 1, 2008, further updates to the
- labeling involving pediatric safety. There was the
- safety study that talked about the 239 pediatric

- patients in a 12-week, double-blind, placebo-
- 2 controlled study, where they were administered the
- 3 Aerochamber with a face mask and improved exposure
- 4 there.
- Again, this mentioned they talked about a
- study comparing placebo to Flovent and it increased
- greater than 3 percent of pyrexia, nasopharyngitis,
- g upper respiratory tract infection, etcetera, as
- 9 previously mentioned.
- 10 (Screen.)
- Moving on to relevant safety labeling, there
- is information about weaning slowly off of oral
- 13 corticosteroids because of the risks of adrenal
- 14 insufficiency, and note is made to watch for
- weakness, nausea, vomiting, and hypertension. The
- warning about bronchospasm is that you have to treat
- with a fast-acting bronchodilator, which Flovent is
- not. Immunosuppression remains at risk and chicken
- pox and measles can have -- just two examples, but
- they can have a more serious, even a fatal, outcome.
- 21 (Screen.)
- There is a drug interaction with ritonavir,

- which causes the Flovent levels to increase or
- $_{\rm 2}$  fluticasone propionate levels to increase and
- 3 decrease serum cortisol levels.
- Again, the warning not to treat a
- 5 bronchospasm with this medication. You need a
- 6 bronchodilator.
- 7 (Screen.)
- Moving on to outpatient utilization data,
- from May 2004 to June 2010 23.1 million prescriptions
- and 6.4 million unique patients. These are
- 11 outpatients and that includes both adults and
- 12 children. Pediatric patients aged zero to 16
- 13 accounted for about 40 percent of dispensed
- prescriptions, 9 million, and about 45 percent of
- unique patients, 2.9 million.
- 16 (Screen.)
- 17 This is just a graph. You can see that the
- -- here's my pointer here, okay. You can see where
- the -- the lighter bars are the adults, okay. So if
- you're just talking about the pediatric population,
- you see a much higher use in the 4 to 11 year age
- range. That's where most of the use is.

Here, zero to 3, 12 to 16, these two lines overlap. Those are actually two lines if you look carefully. It's hard to see if you've got a black and white version of this, because there's a red line

and a green line, but it's similar use.

6 (Screen.)

This is just to note that it's off label to
use in zero to 3. Pulmicort Respules have decreased
over time. The use of Flovent HFA in the zero to 3
year age range has slowly but surely increased over
time.

12 (Screen.)

Top prescribers: pediatricians, 25 percent of the prescriptions; general practitioners, family medicine, doctors of osteopathy, 23 percent. The top diagnosis, not unexpectedly, is asthma, 89 percent of pediatric uses and 67 product of adult uses.

18 (Screen.)

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Moving on to crude counts regarding adverse events for Flovent. Going from the time period May 4, 2004, through August 2, 2010, we have a total of almost 1188 adverse events. And there's 660 in the

- pediatrics You've got 210.
- Where's that button? I can't see it.
- 3 So 70 serious cases, 55 happening in the
- 4 United States. No deaths are noted here. Note here
- 5 there is one death in the null values and that turns
- out to be a pediatric case, so I'm going to talk
- about that.
- 8 (Screen.)
- This is just a bar graph that shows you
- 10 reporting of adverse events. For some reason there
- was a bump in 2006. I don't know why.
- 12 (Screen.)
- So crude counts versus unique cases. There
- were 19 additional reports added for null values and
- that includes one death, which we'll talk about.
- 16 Then we removed 2 duplicates and 15 reports
- associated with the use of other medications, so that
- left us with 212 unique patients.
- 19 (Screen.)
- Now, looking at the pediatric case
- characteristics in this time period, you have zero
- under 1 month, 13 reports 1 month to 2 years, 32 2 to

- $_{
  m 1}$  3 years. Remember, all this is off label. 4 to 11
- $_{2}$  years has the majority of the reports at 148; and 12
- 3 to 16 years, 19.
- 4 (Screen.)
- I wanted to talk briefly about this one
- 6 death that was a null value case. This was a 15
- 7 month old female in Brazil with a history of asthma
- and bronchitis. Flovent was started in September
- g 2009 at 250 micrograms twice a day. 68 days later
- she developed pneumonia, she developed a fever to 41
- 11 Celsius. A seizure occurred, she was hospitalized,
- she died.
- There is no other information about other
- medications she was taking and there was no autopsy
- performed. Causality is not clear in this case.
- 16 (Screen.)
- Moving on to most frequently reported
- serious labeled events, just look at it. I'll just
- let you look at the slide, but you can see the top
- three are asthma, aggression, pneumonia.
- 21 (Screen.)
- Continuing on, personality change, mood

alteration.

2 (Screen.)

Then most frequently reported serious unlabeled events included things like product quality issue, drug being ineffective, and other things ill defined. There's some overdose, insomnia.

7 (Screen.)

Now we move to non-serious -- non-serious -
9 labeled events, and the top players: clearly, cough

10 tops the list; rash, followed by vomiting, and you

11 can read the rest of the list. You can see it as

12 well as I can there.

13 (Screen.)

Non-serious unlabeled events most frequently reported: product quality issue tops the list; drug ineffective, right behind it. Then you see something called tooth discoloration, you see dysgeusia, which means abnormal taste sensation. Then there's dental caries or cavities, and you can see the rest.

20 (Screen.)

So just to kind of summarize the main serious events, both labeled and unlabeled, you have

- your pulmonary events which are labeled, and that pretty much covers asthma, pneumonia, wheezing, coughing, nasopharyngitis. Then you've got your
- 4 psychiatric events and those are primarily labeled:
- aggression, abnormal behavior, irritability, crying,
- 6 mood changing, etcetera.
- Then you have product issues, which are 7 unlabeled, and primarily these involve things like 8 the drug just being ineffective. There were a number 9 of cases of the device being returned to see if it 10 The manufacturer did not find any was working. 11 defects in the product when it was returned, except 12 that one person had some food clogged in their 13 inhaler. 14
- 15 (Screen.)
- I want to speak briefly about some unlabeled
  dental adverse events. We've got 15 of them. Now,
  there were eight cases of tooth discoloration. These
  were in children 3 to 12 years of age, so their teeth
  went yellow, brown, grey, or dark. That was the
  description.
- The dosing range was 44 to 220 micrograms.

- 1 Now, two cases reported resolution of the
- discoloration when the drug was stopped. Four of
- $_{
  m 3}$  eight took medications associated with other dental
- effects, such as albuterol or levalbuterol.
- There were five cases of dental caries,
- again children 3 to 11. Two cases were able to
- 7 report the dose and they were both 440 micrograms
- 8 total daily dose in a 9 year old and an 11 year old,
- 9 which is higher than recommended for age.
- There was then finally two cases of enamel
- anomalies. Both children were four years old. We
- don't know the dose. And there was one case of what
- appears to be a description of enamel erosion.
- 14 (Screen.)
- In summary, this concludes the pediatric
- 16 focused safety review. The FDA recommends adding the
- terms "dental caries" and "tooth discoloration" to
- the post-marketing section, that is section 6, of the
- 19 label. The FDA recommends otherwise continued
- routine monitoring. Does the committee agree?
- 21 (Screen.)
- Finally, I want to acknowledge all these

- individuals and thank them very much for their
- 2 contribution to this presentation.
- CHAIRMAN ROSENTHAL: Thank you, Dr. Elgin.
- Questions from the committee? Yes, Dr.
- 5 Rakowsky.
- DR. RAKOWSKY: This is a more convoluted
- question -- is Carl here, D'Angio?
- 8 VOICE: He stepped out.
- DR. RAKOWSKY: Just a question. If you look
- at the distribution of use, there seems to be an
- eightfold increase in the youngest group, so the zero
- to one year old. The slide that you have, it's sort
- of buried in the zero to three, I think.
- So I'm assuming that the Flovent is maybe
- being used more in, say, a BPD population, where
- you're going to be looking at longer term use of this
- inhaled steroid, I guess in place of other options
- that are out there that are now less used.
- There was the four-week study in the 6 to 12
- 20 month olds where they showed a slight decrease in
- 21 cortisol. Has there been any discussion about a
- longer term study in, like a say, a BPD population,

- considering that there appears to be a rise in the use of this in a young group, where you may be missing signals because the BPDers by nature are going to have some growth problems, get recurring infections, etcetera. So there may be a lot of noise in there where people are sort of saying, oh, that's just them being a BPDer, where the growth suppression may actually be due to the use of this medication.
- 9 That's why it's sort of a convoluted 10 question. Has there been any talk about a longer 11 term study in that population per se?
- May I add to what you just DR. GOLDSTEIN: 12 said? I don't know that we can assume it's BPD. 13 could easily be post-RSV in that population. 14 guess I would suggest maybe asking if it's possible 15 to narrow down exactly what it's being used in, in 16 the majority of the population, is it being used for? 17 Is it in an acute setting or chronic disease? 18
- Then your comment, if it's more chronic, would be very appropriate.
- DR. RAKOWSKY: We do have the four-week safety study, so there is good information there that

- that's what it's being used for.
- And there's Carl.
- CHAIRMAN ROSENTHAL: Dr. Durmowicz, are you
- going to jump in at some point?
- DR. MURPHY: I'd like them to introduce
- 6 themselves again.
- 7 CHAIRMAN ROSENTHAL: Please introduce
- yourselves again for the committee, for the record.
- DR. TONY DURMOWICZ: I'm Tony Durmowicz.
- 10 I'm a pediatric pulmonary critical care physician
- 11 who's in the Division of Pulmonary Allergy and
- Rheumatology at the FDA.
- I was going to take a stab, and I think that
- 14 clinicians here know that many inhaled
- 15 corticosteroids in general, including Flovent, are
- used commonly off label for indications younger than
- the labeled indication of asthma at four years and
- above.
- 19 Your question I think revolved around doing
- 20 additional studies to look at growth and HPA access
- impairment, I think, in younger children. I think
- that those types of studies have been done and they

- are on the label. But we know that if you look at comparison groups there is no real significant effect on HPA access in the groups as a whole.
- However, since people have different 4 the effects of sensitivities to corticosteroids, 5 there are outliers, that certain sets of populations 6 have more of a corticosteroid effect and would have 7 an HPA access potential effect. 8
- With regard to the growth, the growth 9 studies that we do are extremely detailed in a very 10 specific population. They typically don't include 11 the younger kids. You want to do the growth where 12 the growth is about as linear as you can make it. 13 That's typically about four to eight years or age. 14 You don't want to get people that are getting into 15 puberty, you don't want younger kids because they 16 grow faster. So that's when the growth studies are 17 done, and that's the class effect for corticosteroids 18 that we all know about for any inhaled drug. 19
- That's the general kind of answer to what you were kind of questioning about. I hope that helps a little bit.

DR. MELINDA WILSON: If I could potentially comment on the reasons for use, at least for the post-marketing safety data that we evaluated, in the patient population under the age of four the majority of patients received Flovent HFA for the treatment of asthma. So there were 45 cases in that group. 35 out of the 45 received Flovent for asthma.

CHAIRMAN ROSENTHAL: Thank you.

2.1

Dr. Shwayder and then Dr. D'Angio.

DR. SHWAYDER: I'm trying to get my arms around the dental cavities in inhaled steroids. I don't do this on a daily basis, but I see kids, mainly in beautiful downtown Detroit, which is a fairly poor population, and the amount of dental cavities is high. I wonder if any of this sort of data is correlated with socioeconomic or even zip codes, as opposed to just sort of raw data.

DR. MELINDA WILSON: There's an extensive review of the literature contained in the review. It contains 27 articles which evaluated the prevalence of dental caries in patients with asthma versus controls. And in the studies which evaluated

- socioeconomic factors as well as dental hygiene,
- there did not appear to be an association with either
- $_{
  m 3}$  of those factors and the development of dental
- d caries.
- However, in connection with asthma there was
- a higher prevalence of dental caries. So in one
- 7 study it actually noted that patients with asthma
- 8 tended to have better dental hygiene. Potentially
- 9 one might suggest it could be related to the
- information and the labeling that suggests patients
- should wash their mouth after they take, they inhale,
- 12 corticosteroid. And of course, in those patients
- they actually have a higher rate of dental caries.
- 14 The literature is actually rather interesting, so
- certainly worth a look.
- DR. MURPHY: It's on page 17 of your adverse
- 17 event review. There's a quick summary of the
- 18 literature in there for you. The Safety Division was
- 19 actually able to pick up this point, have the
- 20 meeting, and then go back and do another literature
- review and get it in your review for you.
- I bring that up because you're going to hear

- about later one we didn't get in your review for you.
- 2 CHAIRMAN ROSENTHAL: Thank you.
- 3 Dr. D'Angio.
- DR. D'ANGIO: I'm sorry, I slipped out for a moment. But the implied question when I walked back in is, are noeonatologists using this drug. The answer is yes, and that's true, I think, of all of the inhaled steroids for kids what have significant bronchopulmonary dysplasia.
- I'm also interested in the dental caries
  data. I don't have a specific question, but I wonder
  whether -- about the current data. But I wonder
  whether there are other plans to look at those data
  going forward.
- DR. McMAHON: Well, I think we looked at the 15 AERS data regarding this and there's a significant 16 amount -- as Dr. Wilson referred to, there's a 17 significant amount in the literature already, and 18 there have been a number of studies in this area. 19 But my assessment is that there are still a lot of 20 unanswered questions in this area related to 21 asthmatics with dental caries in general, what 22

- $_{1}$  contribution is which drug that they may or may not
- be taking. There's a lot of polypharmacy.
- 3 CHAIRMAN ROSENTHAL: The agency is
- 4 recommending the discussion of dental caries and
- 5 tooth discoloration, as noted on one of the latter
- slides in this presentation. So it is something that
- 7 the agency is focused on.
- 8 Dr. Santana and then Dr. La Russa.
- DR. SANTANA: My question also is related to
- the dental adverse events. I'm not a chemist, so I'm
- not familiar with the HFA propellant. But is that
- 12 chemical entity associated with any issues with
- dental problems? It may not be the drug. It may
- 14 have something to do with the vehicle, because
- obviously teeth are growing tissues, although people
- don't realize they are, in kids.
- So I want to turn the question to the other
- side: Is it the vehicle and not the drug? And do we
- 19 know anything about that chemical in terms of its
- 20 potential impact on dental issues?
- I don't want an answer. I'm just posing it
- as a possibility to consider.

- DR. TONY DURMOWICZ: No, I don't have any
- information on that. But you bring up a good point.
- 3 It's interesting that the Flovent comes in several
- $_4$  different formats and the format that has lactose in
- it, which is sugar, doesn't have a dental caries
- thing going on. So it brings up a point.
- 7 CHAIRMAN ROSENTHAL: Dr. La Russa and then
- 8 Dr. Wagener.
- DR. LA RUSSA: I want to go back to the
- growth issue again. I can understand why you might
- 11 want to study this during a linear growth phase.
- 12 It's easier and probably more reliable, and also the
- possibility that you might blunt the effect of a drug
- during a rapid growth phase.
- But the other possibility is that use of the
- drug during a rapid growth phase may have an actual
- overall greater effect than it does in the linear
- phase, if you study the drug long enough. So I guess
- my question to you is, is there any information about
- what happens during rapid growth, and are there any
- long-term studies to see overall effect on height
- 22 over time?

- DR. TONY DURMOWICZ: I don't think we do
  have any information on other periods of rapid
  growth, if you will, the one to four year population
  or something like that, which would be the off-label
  population for this drug.
- The long-term outcome with regard to the use б of inhaled corticosteroids in individuals or children 7 inhaled corticosteroids seems that take to 8 concluded that final adult height is not 9 medical significantly reduced. That's general 10 literature, not FDA type literature. But other 11 people can comment as well on that. 12
- 13 CHAIRMAN ROSENTHAL: Dr. Wagener.
- DR. WAGENER: Ι actually have 14 questions/comments. The first and maybe milder one 15 is related to device. Is there any way within the 16 AERS system or where you're collecting this data, 17 where you get any information as far as if a device 18 was used to administer this? As you note from one of 19 the studies, when a valve holding chamber is used, it 20 changes quite dramatically the delivery of this drug. 2.1 And I imagine there are other devices with other 22

- drugs which would have a similar point. 1 decreases the deposition within the mouth. 2.
- if we're seeing problems with dental 3 it seems it's extremely important to know whether the drug is being given with one of these 5 valve holding devices or not. My guess is that AERS 6 doesn't have anything even asking that question, and 7 I would challenge the FDA to maybe look at your form 8 and say, should we be adding this for drugs that are 9 given through special devices in order to get that 10 information so in the future we'll know that answer. 11
- So that's sort of, like I say, a question 12 and statement together. 13
- DR. MELINDA WILSON: Thank you for your 14 question. That's certainly a very interesting point. 15 I can tell you from all of the 15 cases that involve 16 dental events, none of the narrative reports describe 17 delivery through, say, а spacer or any 18 additional device aside from the Flovent HFA MDI.
- However, the absence of that data doesn't 20 necessarily mean -- the patient could have been using 2.1 a spacer at some point in time during therapy. 22

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answer, I guess, the first part of your question, the voluntary nature and the spontaneous nature of the adverse event reporting system doesn't necessarily systematically capture information such as the use of a spacer or other device. But that's certainly an area of improvement.

2.1

DR. WAGENER: So that's why -- and more and more drugs that are being approved now do have device relationships. Again, I would suggest that maybe you look at the form so that it's not an elective, but there's a very specific point placed on the form that says, was this drug given by a special device or through a device or something. You could have that for all your drugs.

## CHAIRMAN ROSENTHAL: Dr. Cope?

DR. COPE: Actually, just -- it was not in the review, but we are getting more and more so that we like to screen drugs and devices together as they're used. So we did independently within our office look on the MOD database, which is devices, to see if any Flovent-related cases came up, and there were just a couple. So there was no -- there were no

- real dental or other issues of concern that were in
- there. Again, it's a passive system.
- DR. WAGENER: I think that's a passive
- 4 problem.
- DR. COPE: It is, it's a passive system.
- DR. WAGENER: Because I would never even
- 7 think of talking about dental stuff if I was using a
- device or not.
- 9 DR. COPE: Exactly.
- DR. WAGENER: My second point is I guess I
- 11 would like to say much more emphatic, and that is
- that when you went through all of the different, the
- 13 reams of information we had to look at for this
- program, this report and this drug raised my greatest
- 15 concern. Maybe it's because I'm the only other
- pediatric pulmonologist in the room here. I think
- there are only two of us.
- But it raised huge concerns in me, and it's
- 19 for two reasons. One is that the use data shows a
- significant increase, particularly in the under one.
- But in the group, a quarter or 20 percent of the
- drug out there is being used in less than three year

- olds. This is an age population where to my
- knowledge there's no good data suggesting efficacy.
- 3 It's used because it's used in older patients.
- Then we're identifying two potential major
- side effects. One is tooth decay. In zero to three,
- there is no data on oral or dental issues related to
- inhaled steroids, and yet that's a principal time of
- early tooth development. So we don't know if this is
- g affecting that.
- The second is related to growth, where, as
- Dr. Durmowicz pointed out, all the data comes from
- sort of the 4 to 12 year old or 4 to 10 year old.
- 13 And yet the highest growth velocity in your entire
- life occurs between age one and two, and we have no
- data to tell us whether or not this is altering
- velocity of growth, not where you're going to be when
- 17 you're 10 or 12.
- So it highly concerns that it's used
- extensively and it's used at a time where we have no
- data, where you would expect maybe the highest risk.
- 21 So my gut feeling from this was there should be
- something out there that either warns people, beware

- in under three year olds, or somehow tries to slow
- down the growth of use in this group until we at
- 3 least get some data beyond a two-week safety study or
- $_{4}$  a one-day study that shows that if you give it with a
- 5 holding chamber it's different than otherwise.
- So I don't know what can be done or what can
- be recommended, but I just think this is hugely
- 8 concerning.
- DR. MURPHY: Well, you earned your money
- 10 today. Thank you, because we needed to have an
- additional pulmonologist at the committee because one
- of the things that we are caught in because -- how
- can we get this data? If you go to our -- and I ask
- the division, the Pulmonary Division, to please jump
- in here. But they don't want to increase use in the
- younger, so they're not asking for studies in that
- younger age group.
- So you are then going to have to figure out,
- 19 is this going to be a safety requirement for
- something that's off label, that the sponsor is not
- seeking the -- do you see what I'm saying? So that's
- where you get into what our authority is and how we

- can get it done. We're not saying it can't be done.
- We're just saying I think this is a really important
- point that you're bringing up. We do present this
- use data to you for just this reason. We're getting
- studies done in some of the population, but obviously
- there still continues to be a lot of off-label use in
- 7 populations that aren't getting studied.
- 8 So let me just ask the division if they have
- g any thoughts about how we might get some of that
- without doing something you don't want to do, which
- is encourage the use.
- DR. TONY DURMOWICZ: I think what you're
- hearing Dianne say is there's a clash between the
- 14 regulatory charge that we have and what you would
- call the practice of medicine, because the practice
- of medicine dictates that any approved product can be
- used by an individual practitioner for an indication
- that he or she sees fit. And in Flovent and in other
- inhaled corticosteroids for this younger population
- of multiple diseases, whether it's post-viral,
- whether it's chronic lung disease of the newborn or
- whether it's something else, it's used very, very

1 frequently.

It is a regulatory problem, and one way to 2 try to limit, or can you limit, or how should you 3 limit, from a legal standpoint the use of a drug that 4 is being protected under the practice of medicine to 5 be able to be used as somebody sees fit. So it's a 6 conundrum that we have and we deal with all the time. 7 If you've got some ideas or something like that, 8 that would be okay. 9

10 CHAIRMAN ROSENTHAL: Dr. D'Angio, Rakowsky,
11 and La Russa.

DR. D'ANGIO: I'll defend try to 12 neonatology colleagues to at least some extent. 13 There are not terribly persuasive data, but at least 14 suggestive data, in infants either at risk 15 bronchopulmonary dysplasia or who have 16 bronchopulmonary dysplasia, that inhaled 17 corticosteroids of one sort or another may at the 18 least spare the need for systemic 19 corticosteroids, which have many, complications and 20 are really fairly heavily discouraged in use 21 infants at all because οf premature the 22

neurodevelopmental problems with them.

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One of the things that might help to sort out some of the concern about how these drugs are being used might be to get a better handle on the finer-grained idea of the diagnoses or the conditions for which they're being used, because I don't treat kids with asthma, with wheezing, over the newborn period and I have no idea how practitioners are using those drugs at that time. It might be that the problem would be very different if the use was largely for an indication that's been studied and where there's not been shown to be any efficacy, rather than for an indication in the very young infant, where it has been studied and at there's the possibility of sparing some other, even more toxic, drugs.

That either might make folks very concerned that the use in neonates is only a tiny part of it and there's a huge off-label use in a population where the drug has been shown not to be effective, or it may be that a fair amount of that signal is coming from a very specific use that isn't related to the

- asthma, isn't very closely related to an asthma
- 2 indication at all.
- 3 So those are the only thoughts I can add to
- 4 this.
- 5 CHAIRMAN ROSENTHAL: Dr. La Russa.
- DR. LA RUSSA: So just a suggestions. There
- 7 are a number of NIH-sponsored pediatric clinical
- 8 trials networks that have been given the charge to
- g sort of expand the types of studies that they're
- 10 doing outside their particular areas of interest.
- 11 Those might be the sort of trials networks that you
- could approach with this question.
- Similar questions have come up with, for
- example, anti-retroviral agents and particular drugs
- that are used to treat psychiatric conditions, where
- there's a lot of stuff that's done that's off label,
- 17 and there are studies to try to get some
- 18 pharmacokinetic and some safety data on the
- 19 combinations. So you might think about approaching
- other partners.
- 21 CHAIRMAN ROSENTHAL: Dr. Wolfe --
- DR. MURPHY: I did want to just make a

- comment, that we do work with NIH, NIHCD, on an
- annual prioritization of products that need to be
- 3 studied that fall into these various categories that
- a nobody's going to study them otherwise. So that is
- an outlet that we do try to utilize.
- But it would have to get into that priority
- 7 listing process.
- 8 CHAIRMAN ROSENTHAL: Dr. Wolfe, and then,
- p Dr. Wagener, you're on deck.
- DR. WOLFE: The answer to this question is
- probably no, but, given that year-in, year-out it
- looks like a couple hundred thousand prescriptions
- being written for Flovent for the zero to three, has
- 14 Glaxo discussed with you or in fact submitted any
- kind of attempt to get additional age range covered,
- as in proposing to do clinical trials for this age
- 17 range? Or has whoever makes Pulmicort done the same
- thing, because they are also even larger numbers of
- prescriptions in the zero to three age range?
- DR. TONY DURMOWICZ: I don't actually know
- that off the top of my head, and I'd be doing
- 22 everybody a disservice if I made a guess one way or

- 1 the other.
- DR. WOLFE: If somebody could find it, it
- 3 would just be very interesting to know whether they
- want to actually study this group that is making up a
- 5 couple hundred thousand moderately expensive
- 6 prescriptions a year.
- 7 DR. TONY DURMOWICZ: I will just go back to
- a point that Dr. Wagener and Dr. La Russa were
- 9 making. It was just pointed out to me, and I didn't
- bring it up, that on slide 8 where it says "Studies
- in patients less than four," there was a year-long
- basically growth study done in patients one to three
- years of age. So it wasn't in that linear phase. It
- was in the more rapidly growing population, where
- they have 2.5 centimeter less growth.
- DR. WOLFE: Was that a company study?
- DR. TONY DURMOWICZ: I don't know what FAS-
- 18 309 is. I'm assuming it was a company study because
- people don't tend to do growth studies without us
- telling them to do them.
- DR. LA RUSSA: That's why I brought up the
- point, because of that.

- 1 CHAIRMAN ROSENTHAL: If you're going to make
- a comment -- thank you.
- Are there other comments? Yes, Dr.
- ⊿ Goldstein.
- DR. GOLDSTEIN: This is a question for
- Dianne, if you have a second.
- 7 DR. MURPHY: Sorry. I was trying to find
- out what they're doing at NIH. We're on the list.
- DR. GOLDSTEIN: My question, Dianne, is that
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  m 10}$  we often see the route of approval under the
- pediatric written request where it's been studied in
- adults and found efficacious, and then in an older
- child group, and then PK-PD studies are done in the
- young child age group, albeit in this case it doesn't
- go down to zero, but in the younger group.
- Is there a -- and I think I know the answer
- to this, but is there an option when issuing a
- written request to gain pediatric exclusivity to then
- go back at a later date and say, you know, we really
- should have included some of these younger, some of
- the younger age groups that we're now seeing a lot of
- activity in? It seems to me that we have this

scenario not infrequently and if we had it to do over again or maybe if the written request was written differently, there may be an option to hold the industry to this.

I may be drummed out for saying this now.

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DR. MURPHY: Well, the answer is yes and no. There is a second exclusivity after they get their big one on the moiety, which is the one that usually drives the whole process, where they could come back and get it for another exclusivity.

But when we're talking about pediatric exclusivity, the thing that really drives it is the moiety. We try to think of, in that written request, as many potential uses or indications that are appropriate at the time. But we're in an everchanging situation, because when we began this process in 2000 -- well, in 1997, when we began this process, we had such little information that we ended up issuing a number of written requests where we did not go down into the neonate, where we may not have even gone down to the young child, because we didn't have enough safety data, we didn't have enough

- dosing, we didn't know if it worked.
- 2 We could not ask for a written request that
- 3 went from adolescents neonate for a variety of
- reasons, one being safety, two being end points. We
- 5 weren't ready.
- So in a way -- and I think we've told the
- 7 committee this -- we sort of shot our best chance by
- not getting the younger age group. We've stated this
- 9 publicly. We're at the stage now, you know, many
- 10 years later, where we would like to ask for more
- neonatal studies, our younger age group studies, but,
- as you heard, we're not sure what the end point is.
- Now, in this situation I don't know that
- that's the problem. But I'm just in general saying
- our problem is that we've already used up our
- exclusivity or we're still to this day not sure what
- the end point is. And so instead of holding up the
- written request for the rest of the age populations,
- we'll go ahead and issue it without that neonatal
- 20 population.
- Your question about can we hold up the
- granting of exclusivity --

- DR. GOLDSTEIN: No.
- DR. MURPHY: No, we can't.
- 3 DR. GOLDSTEIN: I'm not asking that.
- DR. MURPHY: Okay, okay.
- I'm asking if maybe -- I DR. GOLDSTEIN: 5 understand what's happened has happened. But maybe 6 going forward with new moieties that are being 7 approved, even if there isn't any foreseeable or 8 current use in the neonatal population, if you can 9 leave that open, still grant the written request on 10 whatever you think they need to do, but if at such 11 time with utilization review it's seen that other 12 pediatric populations are having significant use, we 13 may come back and request such-and-such. 14
- You know what I mean? Going forwards.
- DR. MURPHY: We obviously will think about 16 One of the things with the written request, it. 17 though, is that you put times in it. You want the 18 data to come in in a reasonable period of time. 19 we do ask, we do ask for studies that can come in at 20 different times. So we do do that, and they don't 21 get the exclusivity until they get all of them in. 22

But I'm not sure how you could possibly frame this -- remember, this becomes a legal discussion -- that, well, we want to hold the place here in case we have new information or we want to ask you something later and you can't get your exclusivity until maybe you do that. that would be the problem I think we would have.

CHAIRMAN ROSENTHAL: So let me refocus us a little bit. We've gotten off into a discussion about process, but I'd like to bring us back specifically to this product. Are there other points related to the safety review of this product that need to -- that we need to discuss?

Yes, Dr. Wagener.

DR. WAGENER: So, Dr. Durmowicz asked for suggestions on what they might be able to do. One that I might suggest, is it possible within the package insert to put a warning? The warning would be that in children less than four -- and this is based on the fact that 20 percent of the AEs reported are in kids less than four. So we have a signal here that's telling us there's a risk. But make the

- statement that in children less than four data on safety -- there is no data on efficacy and data on safety demonstrates concerns.
- Specifically, you pointed out the one-year study where the growth was an inch shorter in a three year old. Now, three years olds -- if you're an inch shorter and you're six feet tall, that's not too much. But if you're an inch shorter and you're normally 25 inches tall, that's significant and it's a concern.
- So growth is one. There's no data out there

  on tooth issues and tooth growth, and yet there's

  concern in older patients.
- So I would argue that maybe what needs to be added directly to the pharmaceutical industry is a warning that needs to be added to the package insert that needs to state that lack of efficacy proven and evidence for adverse events, significant adverse events.
- 20 CHAIRMAN ROSENTHAL: Dr. Mathis.
- DR. MATHIS: I'm sorry. I just want to make one clarifying point about this particular written

request, because it actually was one of the written requests where we asked for an extensive amount of studies on this moiety. We asked for the topical cream for atopic dermatitis, we asked for the nasal spray for allergic rhinitis, and we also asked for the inhaled for asthma.

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At the time that this written request was issued, under the law we couldn't actually issue indications that were both on-label and off-label on the same -- in the same written request. So that may have been a reason why we didn't catch the off-label indication within this written request.

Today, because of the change in the law, if we were to issue this written request we would certainly look at the use and say: Boy, what's happening under four? There's clearly a need for data to be obtained. So I think today we would actually have asked for studies in the younger patients, while when this written request was studied we didn't have a mechanism in order to do that.

So I just wanted to make sure people didn't think that they had only done studies in asthma four

- and older.
- DR. MURPHY: She's trying to say they did a
- $_{
  m 3}$  lot of studies that were in the written request and
- that at that time the limitations were such.
- DR. WAGENER And they didn't show efficacy.
- DR. MURPHY: Sorry?
- 7 DR. WAGENER: And they didn't show efficacy.
- 8 600 and some patients and they still couldn't show
- 9 efficacy.
- DR. MURPHY: And I think, though, the other
- quandary we're still stuck with, though, is that we
- often see use in a younger population and we still
- have to make all those decisions about how much is
- the use, is there a safety signal, what is it that
- we're asking them to do. Do we want them to prove
- efficacy or is there really a safety signal we want
- them to go after?
- So I would ask that -- you brought up a
- recommendation that's more than what we're
- recommending. So I think, Geof, you're going to have
- to put that. Is it just pediatric pulmonologists who
- think this or are there other members? I think you

- have to change the question. I hate to say it again,
- but the committee did make an addition.
- 3 CHAIRMAN ROSENTHAL: Dr. Wagener, perhaps
- 4 you can best articulate the recommendation that you
- 5 would make. Are you suggesting that the label be
- changed to make a statement about lack of efficacy
- and the presence of risk in the less than four year
- 8 old group?
- DR. WAGENER: Well stated. Yes, I think
- there ought to be -- again, I don't know what
- technique there is that FDA has for this, but that we
- ought to suggest that there be an addition to the
- label warning the lack of efficacy and evidence of
- adverse events in this age group.
- Then second to that, I would encourage
- 16 whatever techniques possible to encourage further
- study, either through the NIH or what other system
- 18 you have for that.
- 19 CHAIRMAN ROSENTHAL: Yes, Dr. Wolfe.
- DR. WOLFE: I would modify it slightly.
- 21 It's not just the lack of efficacy. There were
- studies, one small, two moderate sized, that failed

- 1 to show it works. Lack of efficacy using 1962
- efficacy law could mean you never studied it. Here
- they studied it. Presumably, if it worked they might
- have sought approval for it. But it didn't work,
- 5 they didn't seek approval, and there are several
- risks that are clearly there in this age group.
- 7 CHAIRMAN ROSENTHAL: Yes, Dr. D'Angio.
- DR. D'ANGIO: Just looking back at the
- g slides here, the efficacy in ages 4 to 11 is
- 10 extrapolated from adult data, and the studies in the
- 4 to 11 year olds that are listed here, at least, and
- 12 I'm not extensively familiar with this, either don't
- appear to have examined efficacy or don't appear to
- 14 have shown it.
- DR. WAGENER: From a pediatric pulmonologist
- 16 perspective, what I would throw in there is that
- asthma in the 4 to 11 year old is not too dissimilar
- from the adult. So one might imply that it would be
- 19 there.
- Of interest, asthma in the under four year
- old is a distinctly different disease, and that's
- 22 more understanding why it wouldn't work in the

- 1 younger child. So extrapolating from the adult down
- to that mid-age group I don't see big problems with.
- 3 Extrapolating down to the infant, three year old, I
- 4 think is more problematic.
- 5 But that's just editorial.
- DR. MURPHY: Well, we can get into a whole
- discussion about extrapolation, but the division felt
- 8 they were comfortable doing extrapolation for that
- g age group. But here's what the label says. It's
- 10 page 10 of the label. On the pediatric use -- I just
- 11 want to make sure everybody knows what's in there
- already -- which is, it says:
- "Safety and effectiveness for Flovent in
- 14 children four years and older has been established."
- 15 It says: "Safety and effectiveness of Flovent HFA
- 16 in children younger than four have not been
- established." And it says: "Use of Flovent HFA in
- 18 patients 4 to 11 is supported by evidence from
- adequate and well-controlled studies in adults and
- adolescents 12 and older."
- So the basis of that is in here. The not --
- 22 I'm just asking. You're saying you want something

- more prominent than just in this statement now, that
- in the under age it hasn't been studied, is what you
- 3 really want to say.
- DR. WAGENER: Well, I'm linking it with the
- 5 AEs. I'm linking it with the fact we see a bunch of
- 6 AEs in that age group.
- 7 DR. MURPHY: Yes.
- DR. WAGENER: And having it simply sit there
- and say it's not been well studied under four --
- DR. MURPHY: Yes, not been studied. We
- 11 haven't shown --
- DR. WAGENER: We ought to add that it has --
- DR. MURPHY: We've haven't studied it and
- it's not been shown because we haven't studied it,
- and in addition. So you have no known benefit and
- you have adverse events, is what you're asking us to
- highlight in the label. Okay.
- CHAIRMAN ROSENTHAL: I think that what I was
- hearing was a suggestion that the language be even
- stronger, that it say -- that it says something to
- the effect that these studies have been done, that
- they have failed to demonstrate efficacy, and that

- $_{
  m 1}$  there are safety data that suggest that there may be
- 2 risks.
- DR. MURPHY: Yes, because there's a whole
- section on the under one, under four year old, in the
- label, too, talking about what the studies didn't
- show. So you're wanting what Geof is saying right
- now, then, something stronger, okay.
- CHAIRMAN ROSENTHAL: Further discussion on
- 9 this recommendation?
- 10 Would you like us to vote on this
- 11 recommendation?
- DR. MURPHY: I think you should, yes.
- 13 CHAIRMAN ROSENTHAL: Further discussion
- 14 before we vote on the recommendation that the label
- be changed to indicate that studies have been
- 16 performed, that they have failed to demonstrate
- efficacy, and that there is safety signal?
- 18 (No response.)
- 19 CHAIRMAN ROSENTHAL: No, okay. All in favor
- of making this recommendation, please raise your
- hands.
- (A show of hands.)

CHAIRMAN ROSENTHAL: All opposed? 1 (No response.) 2 CHAIRMAN ROSENTHAL: Any abstentions? 3 (No response.) 4 DR. SHWAYDER: Abstention. I'm too confused 5 on the data to give a proper response. Are you 6 saying between zero and four it hasn't been shown? 7 DR. LA RUSSA: Zero to four. 8 DR. WOLFE: Zero to four, and they did the 9 study specifically for asthma? They did the study 10 specifically for asthma and there was either no 11 signal or lack of efficacy? 12 DR. MURPHY: Or one to four. 13 DR. LA RUSSA: One to four. 14 DR. SHWAYDER: I was going through here 15 trying to find it. 16 DR. TONY DURMOWICZ: There is no indication 17 for patients zero to four years of age for any kind 18 of asthma diagnosis. There was a study -- and you'll 19 see that in slide number 8 at the top -- with 359 20

children one to three years of age, for asthma.

outcome was asthma symptom scores and there was a

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- 1 significant decrease in asthma symptom scores.
- 2 However, they do not have an indication for the age
- group of one to three to treat asthma.
- DR. SHWAYDER: So we're making a comment on
- 5 something --
- DR. WAGENER: Then there's a second study,
- y which is the third one there, with 629 patients, and
- 8 the statement is both groups with improvement in
- g asthma, trend favoring one drug over the other.
- DR. SHWAYDER: That's a growth study.
- 11 Typically, both groups have steroids on board, and
- you can't say anything about efficacy in that.
- 13 CHAIRMAN ROSENTHAL: So I don't feel like I
- $_{14}$  have got the -- the task that we faced today was
- exploring some of the safety data. I don't think --
- there's probably more efficacy data or information,
- that if we were going to be debating efficacy that
- would come to the table. Do you guys agree with that
- or not? You think this is it?
- I'm asking the agency.
- DR. MURPHY: I think -- correct me,
- 22 division, but I think what we heard was that we

started out in discussion of safety for the kids it
was studied in, and we heard for this one to three
year old, where we didn't have -- one to four, that's
what it says in here -- where we don't have really an
approved indication, but even more so the fact that
there's a lot of use in this younger age group where
there is no label is a safety concern.

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DR. WAGENER: Pick up on the safety.

DR. MURPHY: And that you would like us to try to get it studied in that population, because of the reasons that have been brought forth, but realizing our limitations that right now the thing that one can do, and I think you're proposing, is in the face of not having those studies that we label it -- my grammar's failing me -- that we have more prominent labeling.

CHAIRMAN ROSENTHAL: You're on the right path. You're on the right path. I think there's a sense that there is an imbalance between the efficacy data and the safety data, and that that imbalance, if we have a correct impression, that that imbalance needs to be addressed in the label.

- DR. SHWAYDER: Are you including the dental
- data in your statement or just like the growth and
- 3 non-efficacy?
- CHAIRMAN ROSENTHAL: No, I think the dental
- data -- well, I'm not writing the statement, but I
- 6 think the dental data is something that has the
- attention of the agency.
- DR. SHWAYDER: That was the original
- g question on the slide.
- DR. TONY DURMOWICZ: The dental issue's
- already been addressed with the company and they're
- going to propose -- we proposed to them to add dental
- caries to the label already, and we'll be getting
- something back from them some time and looking at it.
- So that issue's being taken care of.
- 16 What you're discussing here I think is a
- broader issue on what to do with safety issues and
- not approved uses.
- 19 CHAIRMAN ROSENTHAL: Now, can we go back to
- slide 29, because I think this question also needs to
- 21 be modified in some ways. My sense is that the
- 22 committee would concur with a recommendation to

- continue routine monitoring, with the caveats being 1 that we would like the agency to consider -- to take 2. another look, a good hard look at the label, and make 3 sure that it's worded in a way that will effectively deliver the message that's been articulated; and also 5 that the agency do whatever is within its means and 6 whatever can be accomplished to try and promote 7 further study in kids younger than four. Is that one 8 of the messages that's come out? 9
- Okay. So that's a long way of making a statement, but do people concur with that? Let's raise our hands if we concur with that sort of longwinded statement?
- 14 (A show of hands.)
- 15 CHAIRMAN ROSENTHAL: Then anyone opposed?
- 16 (No response.)
- 17 CHAIRMAN ROSENTHAL: Any abstentions to
- 18 that?
- 19 (No response.)
- 20 CHAIRMAN ROSENTHAL: Let's go around the
- table. Dr. Wolfe, will you just acknowledge that you
- supported that idea?

- DR. WOLFE: Sid Wolfe. I support the idea.
- DR. LA RUSSA: I'm a little confused now.
- 3 Are we not voting on the other statement that was
- previously made, about the under four group? We're
- going to leave it?
- DR. WOLFE: Both.
- 7 DR. LA RUSSA: Why are we going to do both?
- 8 CHAIRMAN ROSENTHAL: We already -- I think
- 9 we already voted on the strengthening of the label
- 10 concept -- oh, I see. We raised our hands, but
- you're saying we never went around the room.
- DR. LA RUSSA: Yes. So I'm not sure. So
- you're counting that as a vote?
- 14 CHAIRMAN ROSENTHAL: The system has broken
- down, as you've just pointed out.
- DR. LA RUSSA: I just want to make sure I
- 17 know what I'm voting on.
- CHAIRMAN ROSENTHAL: Let's finish this one,
- and then we'll go back and call that into the
- 20 microphone regarding the recommendation specifically
- 21 pertaining to the label.
- DR. SANTANA: But Geof, I think there was

- 1 concurrence on that previous discussion. So why
- don't we take that concurrence and add it to this
- recommendation and have one vote?
- 4 CHAIRMAN ROSENTHAL: I tried to do that by
- 5 my complex sentence in reframing this.
- DR. SANTANA: Yes.
- 7 CHAIRMAN ROSENTHAL: But there was actually
- not concurrence. There was an abstention.
- DR. WAGENER: Although, if I was looking
- right, I believe in your more complex statement that
- abstention went away.
- 12 CHAIRMAN ROSENTHAL: We won't erase the
- votes, but let me just restate the question if I can.
- 14 I believe the question is would the committee concur
- 15 with an approach that includes the following:
- 16 Continuing routine safety monitoring; encouraging the
- sponsor to consider studies that will further explore
- efficacy in the less than four year old age group;
- and strengthening the label to indicate that studies
- have been done, that efficacy has not been strongly
- demonstrated, and that safety signal has emerged in
- the younger than four age group.

- DR. SANTANA: And in addition, we concur
- $_{2}$  with the dental caries and tooth discoloration things
- 3 that they're already negotiating.
- 4 CHAIRMAN ROSENTHAL: That they were already
- 5 doing.
- Okay, those four points. Everybody who
- your supports that collection of four points raise your
- hands.
- 9 (A show of hands.)
- 10 CHAIRMAN ROSENTHAL: All right. Anyone
- 11 opposed?
- 12 (No response.)
- 13 CHAIRMAN ROSENTHAL: Abstentions?
- 14 (No response.)
- 15 CHAIRMAN ROSENTHAL: Let's go around the
- 16 room. Dr. Wolfe?
- DR. WOLFE: I again support.
- DR. LA RUSSA: I concur.
- DR. WAGENER: Wagener. I agree.
- DR. HOLMES: Greg Holmes. I agree.
- DR. KRISCHER: Jeff Krischer. I agree.
- MS. CELENTO: Amy Celento. I concur.

- DR. SANTANA: Victor Santana. I agree.
- DR. RAKOWSKY: Alex Rakowsky, agree.
- DR. MOTIL: Kathleen Motil, concur.
- DR. D'ANGIO: Carl D'Angio, concur. Geof,
- that was a masterful effort.
- DR. SHWAYDER: Tor Shwayder. I concur with
- your four points.
- DR. TOWBIN: Kenneth Towbin, concur with the
- four points, and appreciate that out of complexity
- 10 sometimes truth emerges.
- 11 CHAIRMAN ROSENTHAL: All right. Dr. Elgin,
- thank you very much for bearing with us and for
- helping us with the deliberation.
- Next Dr. Ellenberg has a statement to read.
- DR. ELLENBERG: At this time I need to make
- 16 an additional statement regarding conflict of
- interest which was not mentioned this morning. We
- 18 would like to note that Dr. Santana will recuse --
- will be recused from the discussion of Neulasta.
- 20 CHAIRMAN ROSENTHAL: Let's move on with the
- discussion of Neulasta. Presenting today will be Dr.
- 22 Alyson Karesh.

Dr. Notterman, please be seated. 1 Dr. Karesh received her medical degree from 2 the Medical College of Virginia and completed her 3 internship and residency at Children's Hospital at 4 Pittsburgh. Prior to joining the Pediatric and 5 Maternal Health Staff in the summer of 2008, Dr. 6 Karesh worked as a pediatric hospitalist at Inova 7 Fairfax Hospital. Additionally, she's worked as a 8 pediatrician for Kaiser Permanente. 9 Thank you very much for presenting today. 10 (Screen.) 11 NEULASTA (PEGFILGRASTIM) 12 DR. KARESH: Good afternoon. I'm Alyson 13 Karesh, pediatrician on the Pediatric and Maternal 14 Health Staff. I'm going to discuss with you planning 15 pegfilgrastim, or Neulasta. 16 (Screen.) 17 By now you're familiar with this outline. 18

You'll note, though, that under adverse events I will

be discussing fatal adverse events, serious non-fatal

adverse events, and then medical errors.

(Screen.)

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1	Pegfilgrastim, or Neulasta, is a leukocyte
2	growth factor, originally approved in 2002. Neulasta
3	is approved to decrease the incidence of infection,
4	as manifested by febrile neutropenia, in patients
5	receiving myelosuppressive therapy.

Let me call your attention to the fact that

Neulasta is not approved for use in pediatrics.

8 (Screen.)

9 Pharmacokinetics, safety, and exposure -10 Pharmacokinetics, safety, and exposure response were
11 evaluated in 37 patients.

12 (Screen.)

The pharmacokinetic results from the pediatric study are shown in this slide. You will note that the terminal elimination half-lives, although variable, was longest in the youngest age group.

18 (Screen.)

In the pediatric study, the most common adverse reaction was bone pain.

21 (Screen.)

Labeling states that safety and

- effectiveness in pediatric patients have not been 1 established and provides the pediatric study results. 2.
- (Screen.) 3
- Now that we have discussed the pediatric 4 study and the resulting labeling, let's discuss 5
- Neulasta drug use. 6
- (Screen.) 7
- 2006 2009, approximately Between and 8 1432,000 patients used Neulasta, of which pediatric 9
- patients were less than one percent. 10
- (Screen.) 11
- The most common prescribing specialty 12 oncology. Pediatrics was less than one percent. 13
- top diagnosis code was neutropenia. 14
- (Screen.) 15
- Now to discuss the adverse events. 16 crude counts are displayed on this slide. You will 17 note there were 27 pediatric reports. This is 18 approximately one percent of the total crude count 19 reports.
- (Screen.) 21

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Of these 27 pediatric crude count reports, 22

- 1 24 were direct exposure non-duplicated.
- 2 (Screen.)
- Of these 24 direct exposure, non-duplicated reports, there were two fatalities and another 17 serious non-fatal reports. Of the 17 serious non-fatal reports, 6 of these adverse events are labeled for adults. As we discussed earlier, Neulasta is not approved for use in pediatrics.
- I want to emphasize that in most instances
  the adverse events appear related to the patient's
  other medications and-or their underlying disease.
- 12 (Screen.)
- This slide describes the two fatal adverse events. One was a 14 year old female with metastatic lung cancer. She had compression of her aortic arch from mediastinal and hilar lymphadenopathy and went into cardiac arrest.
- The other case was an eight year old with a connective and soft tissue neoplasm. Limited details were provided.
- (Screen.)
- The next two slides go over the six labeled

- for adults, serious non-fatal adverse events. The
- first three adverse events, which are listed on this
- slide, are all allergic-type reactions which resolved
- with medical management.
- 5 (Screen.)
- The next three, as shown on this slide, all
- involve elevated white blood cell counts.
- 8 (Screen.)
- Now that we've discussed the six labeled
- non-fatal serious adverse events, we will turn out
- 11 attention to the unlabeled serious adverse events,
- which are described on the following seven slides.
- Because there doesn't seem to be any pattern, these
- 14 cases are presented in order of descending age.
- The two cases on this slide are both
- neurogenic adverse events in 16 year old females on
- 17 chemotherapy.
- 18 (Screen.)
- The first case on s slide is a 15 year old
- 20 male who developed glomerulonephritis. He had
- 21 multiple medical problems, including severe chronic
- neutropenia.

The second case on this slide is a 15 year old female who developed electrolyte abnormalities and hearing loss. Of note, she was on cisplatin.

(Screen.)

This slide describes a 15 year old male with acute lymphoid leukemia on multiple medications, who developed sepsis and ultimately recovered.

8 (Screen.)

The next two cases are a 13 year old male and a 10 year old female who each developed febrile neutropenia.

12 (Screen.)

This slide describes an eight year old with

Ewing's sarcoma who developed tachycardia and

multiple gastrointestinal and respiratory problems,

all believed to be chemotherapy-related.

17 (Screen.)

The next two cases are a six year old with renal impairment, believed to be related to Wilm's tumor, and a four year old with febrile neutropenia and blast cells, believed to be related to lymphocytic leukemia and chemotherapy.

1 (Screen.)

The last unlabeled adverse event case was an accidental overdose related to a medical error, in which the wrong drug was administered.

5 (Screen.)

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OSE then looked further at medical errors associated with Neulasta, and here are the results.

There were 29 total adult medications errors and 3 pediatric ones. The three pediatric medication error reports we will discuss further.

11 (Screen.)

There were two pediatric cases of overdose,
in which each patient received the entire contents of
the prefilled syringe. Both cases resolved.
Labeling for adults states that dosage form and
strength is 6 milligrams per 0.6 milliliters in a
single-use prefilled syringe.

18 (Screen.)

There was one pediatric case of an incorrect route of administration. A 15 year old may have received Neulasta intramuscularly rather than by subcutaneous injection.

Because of these three pediatric medication
error reports that we've just discussed, FDA is
reviewing all of the Neulasta medication error
reports since approval.

5 (Screen.)

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So, in summary, Neulasta labeling contains information from the pediatric study, including that safety and effectiveness in pediatric patients have not been established, and provides the PK data. The pediatric focused safety review identified two pediatric fatalities. One was attributed to cardiac arrest secondary to underlying disease and the other had insufficient information to assess Neulasta's role.

The pediatric focused safety review also identified three pediatric medication errors, two of which were associated with incorrect dosing. So FDA is reviewing all Neulasta medication error reports.

19 (Screen.)

FDA will update the Pediatric Advisory

Committee once the additional analysis of the
medication errors is complete. Pending this

- analysis, please discuss the following options:
- One, no change in labeling;
- Two, remove the pediatric PK information
- 4 from labeling;
- 5 Three, add to labeling information regarding
- 6 pediatric medication errors;
- And four, any other suggestions.
- 8 (Screen.)
- I want to acknowledge the folks listed on
- this slide. Thank you.
- 11 CHAIRMAN ROSENTHAL: Thank you, Dr. Karesh.
- DR. MURPHY: Geof, we want to note in your
- 13 background package is also the medication error
- report for the one year. So that's what we're doing
- now. We didn't have enough time to do it for many.
- 16 We're going back and looking at all possible
- 17 medication errors. So I just wanted to make sure
- everybody understood what they had in hand and what
- they didn't have in hand yet.
- 20 CHAIRMAN ROSENTHAL: Do you mind saying that
- again, Dr. Murphy? What do we have?
- DR. MURPHY: You have, besides your usual

- adverse event review and use review, you have a
- 2 medication error review for those products that were
- 3 -- those cases that were identified in the one-year
- post-marketing. Because -- and division, help me
- here. My understanding is it comes in one prefilled
- syringe type thing. So that's the issue, is that
- 7 it's already prefilled and that's how kids are
- getting a higher dose.
- So what we're doing now is we're going to go
- 10 back and look at a broader sample for medication
- errors. That's the thing you don't have.
- 12 CHAIRMAN ROSENTHAL: Thank you.
- Can the people who just joined us at the
- table please introduce yourselves.
- DR. SUMMERS: Jeff Summers, Division of
- 16 Biological Oncology Products.
- DR. HERNDON: Thomas Herndon. I'm the
- 18 clinical reviewer in Oncology Biologics.
- DR. ABATE: Rick Abate, safety evaluator,
- 20 Division of Medication Error Prevention and Analysis.
- DR. PRATT: Bob Pratt, safety evaluator,
- team leader, Division of Pharmacovigilance 2.

- 1 CHAIRMAN ROSENTHAL: Thank you very much.
- Yes, Dr. Rakowsky.
- DR. RAKOWSKY: Just a question for the 3 oncologists. What would be a typical dose for a 4 young child if you're going to use this? So it's 6 5 milligrams for .6. Are we looking at like a 1 6 milligram? How detailed of a marking would you need 7 on the current syringe or would we be looking at a 8 completely different syringe having to be included in 9 the package potentially? 10
- DR. SUMMERS: For the different age groups, 11 for a neonate or a one year old, I don't think the 12 syringe would be appropriate or applicable. 13 micrograms per kilogram is the dose that they studied 14 in the studies that were presented. So for a 16 year 15 old that syringe might be just fine, but for a 1 year 16 old that syringe probably would not be useful. 17 could extemporaneously utilize that. 18
- DR. RAKOWSKY: So for a 10 kilo child, that would be 1 milligram. So it would be .06. So you're looking at a small volume.
- 22 CHAIRMAN ROSENTHAL: Dr. Wolfe and Dr.

1 Wagener.

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DR. WOLFE: Slide 8 indicates that over the 2 three year period from 2006 to 2009 there were a 3 total of 330 pediatric doses used. Assuming that those medication error data are from the same period 5 of time, that's a worrisome number of medication 6 errors for 330 patients. The pharmacokinetics, which 7 is really all that is established on that age range, 8 shows an extended half-life in that group. 9

The choices that are put before us is to leave the labeling as it is. It does say safety and efficacy have not been established in this pediatric range, but it also includes some information, and I think we're caught between a rock and a hard place, because on the one hand I think we would probably like to discourage use in this age range since safety and efficacy have not established, it has a long half-life and it is much more likely to have medication errors since the dosage form is not meant for this age range.

So I think of these choices here, no change in labeling, remove the pediatric PK information from

- the labeling, which is how people are going to dose
- in this unapproved age range, add to labeling
- information regarding pediatric medication errors --
- d could we just hear from the division or from anyone
- else, Dr. Karesh, which you prefer and why?
- DR. KARESH: I think part of the reason we
- formed the question that we did is that we really did
- want the advisory committee's input on it.
- DR. WOLFE: We'd like to give you input. We
- would like to know what your -- you've looked at this
- much more than we have. Was there some three-way tie
- between these three or is there some inclination by
- the division to go in one of these three directions?
- I just would be interested in hearing that. We will
- still discuss this and give our input.
- DR. SUMMERS: I think the general policy for
- the Office of Oncology Drug Products has been to try
- to include for oncology drugs or even supportive care
- oncology drugs as much information as we can in the
- label with regards to pediatrics, so that they might
- 21 be able to be used thoughtfully and intelligently for
- these severe, life-threatening conditions.

- So that would be the reason that this information was included in the labeling initially.
- 3 CHAIRMAN ROSENTHAL: So for other 4 medications that we've discussed, even ones that 5 don't have pediatric indications, if we have PK data 6 we tend we tend to include that. So the fact that PK 7 data is in this label is not terribly unusual.

Dr. Mathis.

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DR. MATHIS: I would also like to add that 9 the pediatric review committee did look at this and 10 discuss this pretty extensively with the review 11 division and at the time was concerned about the fact 12 that these products were used in very sick pediatric 13 patients, and providing any information may help 14 avoid potential problems and allow people to use the 15 products more wisely. 16

That being said, I think at the time we were not aware of the medication errors. So that's something that's kind of come up as an additional thing to think about in the context of this label.

DR. MURPHY: I want to put it even in a broader context, because earlier today you heard a

recommendation from a committee to put PK labeling in when we have no efficacy. This is a constant tension, an issue for us. If the PK is -- and we do put it in, particularly if we know they're dosing wrong, we know that the dosage that you normally would have done on a per kilo basis is not going to work.

What we try not to do is to put PK data in when we are very confident it was a good study and it didn't work. We'll just say PK was done. This is a different situation. As many of you who have been around for a while, for cancer products we often don't get to phase three, and therefore we put as much information in the label as possible because we often are still -- we have a situation where sometimes actually we can definitively say don't use this, the activity -- actually, the patients died faster on one of the trials, and we'll put that in there.

But there are times with cancer products where that's all the data you're going to get for a while and you're not going to have a big large phase

- three. So I'm saying that because I don't want the committee to go away, particularly some of the newer people, thinking, well, you can fail and we're going to put the dose in there for you to use just in case you want to use it. That's not what we would normally do.
- 7 CHAIRMAN ROSENTHAL: Dr. Wagener.

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- DR. WAGENER: I was going to start out with the question why are you even suggesting number two, removing data that could theoretically be valuable.

  But you've sort of answered that.
  - One thought or suggestion, and that is that currently the prescribing information says that the dose is one syringe. Then under the toxicity data later on, you have that there have been doses as high as 300 mikes per kilo that have been given to patients with safety. Would it be reasonable that when you have a prefilled syringe like this that it says the usual dose is one syringe and then you give the dose range per kilogram? So in other words, this one syringe in the studies that they got it approved with probably had a dose range between 80 per kilo

and 150 or something like that.

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That at least would provide the off-label user a range to have an estimate or a thought or to think of a per-kilo or something of that type. It doesn't quite do what you want to avoid, which is say this is the dose per kilo, but it does maybe get rid of the accidental overdoses where somebody says, oh, the dose is one syringe, and this is a two-year-old child.

DR. MURPHY: Do you have any more insight on the medication errors you want to give to the committee about how they occurred?

DR. ABATE: The medication error, the overdoses did occur because the nurse administering the product gave the entire syringe, thinking that the dose was the whole syringe. We haven't completed our further medication error review yet. But because this product is set up, is designed to deliver the adult dose in one syringe, that's what they're going to give. The dose is .6 mls, which is a very small volume, and even in a smaller child that could be given subcutaneously by a nurse that's not even

- thinking about the fact that there's six milligrams
- $_{\rm 2}$   $\,$  in that .6 mls, not necessarily the dose that needs
- 3 to be recalculated for that child.
- 4 CHAIRMAN ROSENTHAL: In terms of labeling
- 5 options, this almost sounds like an awareness-raising
- issue. If there's not a human factors solution, if
- there's not a way to kind of repackage it, then --
- DR. SHWAYDER: I have to put in my two cents
- because my N equals one experience with this was a
- family member who was a family member who was given
- this to go home and give it to herself the next day
- after her chemotherapy. She asked me to come up and
- give this thing. I'm almost certain this is packaged
- for people to give it to themselves at home.
- DR. SUMMERS: Some patients do give it to
- themselves at home, yes.
- DR. SHWAYDER: So you need to know that,
- because this is a: Dummy, just do this. If you want
- 19 it for the physician, you need to package it in a
- 20 multi-use vial with the PK data. It's just asking
- the pharmaceutical company to do for pediatric use or
- for use other than home use, here is the vial, go buy

it, and use it in your office.

- 2 CHAIRMAN ROSENTHAL: Let's maintain order.
- Dr. D'Angio, Dr. Farrar, and then Dr. Wolfe.
  - DR. D'ANGIO: I just want to respectfully disagree with the folks who are saying we don't want to encourage pediatric use. This is a drug that the reason that it's not labeled for pediatrics is because nobody's done the study, not because there's any evidence that it's not efficacious or even that there's any lack of evidence that it is efficacious. The studies just haven't been done.
    - It's a drug that's very likely to continue to be used in very sick pediatric patients, where the alternative would be a non-pegalated filgrastim that they'd have to get in hospital as opposed to at home.
    - So I disagree with the contention that we want to discourage use of this drug.

Going on from that, then I realize that the company has absolutely no impetus to do this because they would be being asked to do something for an indication that they don't have. But the solution to this, I agree, obviously is a human factors solution

- and making it so that it is possible in some way to
- $_{2}$  deliver the correct dose, because right now -- I also
- have a family member who's used this drug and it is
- set up to give the whole dose.
- 5 So that if one doesn't want to give the
- 6 whole dose, that needs another method of
- 7 administration besides a prefilled syringe.
- 8 Everybody in pediatrics knows that when you get a
- 9 prefilled syringe you give all of it, and that's the
- 10 way we give our vaccines and everything else. It
- takes -- to have a drug packaged in a way and used in
- 12 pediatrics where you have to go against every
- instinct that you have to give all the prefilled
- syringe sets people up for this problem. I wish you
- the best of luck in trying to figure out how to help
- the company solve this issue.
- 17 CHAIRMAN ROSENTHAL: It sounds like this is
- not -- we're talking about this particular product,
- but this issue of unit dosing and overdosing using
- 20 the unit dose strategy in pediatrics is relevant
- across a number of drugs.
- Dr. Farrar, you had your hand up a while

ago.

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DR. FARRAR: Yes, and I would reiterate what 2 he just said, which is this is -- and what the agency 3 is saying, and that is this is not going to get studied. This is going to be -- there aren't a lot 5 of options for these kids. So I think this is -- I 6 I would agree with leaving in the PD7 information. 8

So number three, if you're not approved then how can you -- if there's no labeling information, then how can you officially have a medication error? In other words, if you don't really -- the point of labeling is to say what the dose is. If you don't know what the dose is in kids -- yeah, we think that the whole thing in a two year old is probably not right, but do we know that?

If we don't have -- how can we say that this is truly -- you're going to be -- I don't have to vote on it; you do. But you're going to be voting on whether or not to say there's a medication error when you don't even know what the actual dose in these people should be.

1 CHAIRMAN ROSENTHAL: Dr. La Russa.

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DR. LA RUSSA: Let me propose something that's sort of a combination of this. What you could say is that off-label use of this drug in pediatric patients has resulted in medication errors -- and I'll get to your point -- where the entire vial has been given.

The issue of whether it's a medication error really depends on what dose was written for and whether the whole vial was written for. We give lots of drugs for off-patient -- off-label use, and that's a whole other issue of how individual hospitals handle that. But if the person who wrote the order wrote for the entire vial and then the entire vial was given, then theoretically that's not a medication error. But if they wrote for a per kilo dose and the entire vial was given, then that's a medication error, at least in our hospital.

So here you could say there is PK data in kids, there is no indication for kids, but beware that because the syringe is set up for a unit dose that you may give an inappropriate dose in children.

1 CHAIRMAN ROSENTHAL: Dr. Wolfe.

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DR. WOLFE: I was going to say much like that and just add one thing, which is I think that the label can be strengthened to discourage really misuse in children, not so much discourage use. That would say: This drug has not been adequately studied in children sufficient to have enough safety and efficacy data to have it approved. Therefore, it is not available in what might otherwise be the proper pediatric dosage form. Watch out.

I think that this is sort of in the label now, but I think that there needs to be a bigger warning if you're getting in this tiny population that many medication errors, a bigger warning against doing things like those that have happened. Yes, they're human, but I think that the label could be much stronger and make it clear that this company can't make this available in a pediatric dosage form because it isn't approved for that age range.

The company literally can't do that. The FDA can't approve a pediatric dosage form for something that has not passed muster in that age

- 1 range; is that correct?
- DR. MURPHY: That's correct. There is PK
- data, though. Actually, the numbers were like 11,
- 10, and 13. So it's in your review.
- 5 CHAIRMAN ROSENTHAL: Just briefly regarding
- the statement by Dr. La Russa regarding the intent of
- 7 the person who is prescribing the medication:
- 8 think that's a good point. These came to the
- attention of the agency because they were reported as
- adverse events and so somebody thought something was
- awry in the process.
- 12 Yes, Ms. Celento.
- MS. CELENTO: I guess I don't understand why
- it has to come predosed in a syringe. I mean, it's
- just for ease of use and delivery? Can it just be
- packaged in something, another form?
- DR. D'ANGIO: I'll take a stab at that. It
- is designed for adults to use at home and it's the
- right dose for adults to use at home. That's the
- 20 perfect way -- it's a perfect system in that
- 21 population. The problem is it's used in other
- 22 populations.

- DR. SHWAYDER: So are many others that are
- done the same way.
- 3 CHAIRMAN ROSENTHAL: Dr. Towbin and then Dr.
- Wolfe, please.
- DR. TOWBIN: Would it be too strong a
- statement to say that this method of delivery is
- 7 contraindicated in children beneath a certain age?
- CHAIRMAN ROSENTHAL: Specifically the method
- of delivery?
- DR. TOWBIN: This method of delivery, not
- 11 this drug but this method of delivery is
- 12 contraindicated.
- DR. SHWAYDER: Method is --
- 14 CHAIRMAN ROSENTHAL: Does the FDA have the
- ability -- is the syringe considered a device that
- goes with this medication? Is the syringe that it
- comes in part of the unit that the FDA controls in
- some way or not? I know that for some medications
- that are delivered by a certain type of device the
- device also ends up being scrutinized through some of
- the processes at the agency. Is this one of those or
- is this too non-specific to fall into that category?

- DR. HERNDON: Yes, it is.
- 2 CHAIRMAN ROSENTHAL: I wonder whether maybe
- another way to frame this question or this issue is
- does the agency have the ability to regulate the way
- 5 that this is dispensed to people within certain age
- 6 groups?
- 7 DR. MURPHY: But again, the problem is it's
- dispensed appropriately for the approved indication.
- I mean, your question is can we go out and try to
- 10 make the sponsor to make a different delivery system
- for an unapproved indication? I think the answer is
- 12 no.
- 13 CHAIRMAN ROSENTHAL: Well, I think that's a
- good point. I think that's a good point.
- Hang on. I've got -- Dr. Towbin, did you
- have a question?
- DR. TOWBIN: I just want to reiterate that
- we're not saying that they have to make it different.
- 19 All we're saying is that this method is
- 20 contraindicated in children beneath a certain age or
- size or however we want to say it that we think is
- 22 appropriate.

1	CHAIRMAN ROSENTHAL: Dr. Wolfe and then, Dr.
2	Notterman, did you have your hand up?
3	DR. WOLFE: A kind of elephant in the room.
4	I looked this up yesterday or the day before. Two
5	years ago the cost of this was estimated at \$3,000 to
6	7,000 for one dose. So just in terms of the way it's
7	packaged, if you have a child and you want to give it
8	to them, aside from the issue that you think vaccines
9	are you give them the whole thing, this is a very
10	expensive drug.
11	It works, to be sure, and I think that in
12	terms of what do you do with the .6 ml that's in this
13	unit dose syringe? You don't give the whole thing to
14	little kids, for sure. But what do you do with the
15	rest of it? Do you have to pay for the whole thing?
16	
17	So there are those kind of considerations.
18	I realize the economic considerations aren't
19	primarily an FDA issue, but that gets into the whole
20	problem with the doctor buying this from the company,
21	whatever, and then what do you do with the rest of

it.

1 CHAIRMAN ROSENTHAL: Dr. Notterman.

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2 DR. NOTTERMAN: Thank you. I wanted to 3 return for a moment to the issue of FDA evaluation of 4 efficacy and what the sponsor has done or been asked 5 to do to evaluate or to extrapolate efficacy in 6 children, and then I may have a follow-up question 7 depending on what I heard.

DR. SUMMERS: This particular study was developed by the sponsor, was agreed to by FDA before PREA was even enacted, only a couple years after the pediatric rule was finalized. That's almost a decade ago that the study was initially worked upon.

I think both the FDA and the company pursued due diligence in attempting to initiate, conduct, and complete this study. At the time, good press was good business for Amgen and I think that they were proactive in trying to do this study.

In retrospect, I think the populations in the chemotherapy regimen, particularly sarcoma, Ewing's sarcoma, may have been problematic for the company to actually accrue patients in the younger age groups. I think retrospectively we can look back

- and have some insight on how we might have designed
  the study a little better so it could accrue faster.
- As I pointed out, this occurred before PREA,
  before the agency had a lot of experience necessarily
  with these kind of studies. Granted, the written
  request was available under the FDANC Act, but that
  was not for drugs, not for biologics, and this is a
  biologic. So that whole written request process
  didn't work for this particular drug.
- We acquired PK data. The PK data, because 10 it's a receptor-mediated clearance mechanism, that PK 11 data is highly variable and not very predictive of 12 efficacy at all, so it couldn't be used 13 extrapolate to efficacy. Granted, we also got some 14 pharmacokinetic data, which was the ANC 15 Those ANC counts, the pharmacodynamic data that we 16 had and the PK data that we had when the division 17 reviewed that, we did not feel that that was adequate 18 data to be able to extrapolate to efficacy. 19
- DR. NOTTERMAN: So I think just as -- this is my follow-up question. I think that with the BPCA you have a new mechanism now, am I correct?

- DR. SUMMERS: Actually --
- DR. NOTTERMAN: Let me finish my question,
- g please.
- I think that, unless I'm mistaken in my
- 5 understanding of the Federal Code, which could be,
- that the agency could make a written request for
- further studies. Or am I wrong about that?
- DR. SUMMERS: My understanding, initially
- there was in FDAMA -- that's where the exclusivity,
- 10 pediatric exclusivity, came in with regard to written
- 11 requests. Then that was codified in BPCA. Before
- that there was the pediatric rule that then got
- struck down, and then there was PREA.
- The new biosimilars legislation, which came
- in under the Patient Protection and Affordable Care
- Act, which is the biosimilars legislation, in there
- there's particular statutes that allow for written
- requests to be written for biologics. I can't tell
- you how that's going to work for a biologic that's
- 20 been on the market now for the last 20 years or 15
- years, as to how we could potentially write a written
- request for the company to actually do studies to try

- 1 to get more exclusivity.
- But I'm sure my pediatric colleagues here
- 3 could address that.
- DR. MURPHY: Jeff is exactly correct that we
- do have a mechanism now to issue written requests for
- 6 biologics. But again, one of the problems that
- occurred when trying to study this drug was because
- it is in so many ways the standard of care, it's very
- g difficult to get physicians to enroll patients and
- 10 compare against a placebo. So it would be a
- difficult drug probably to study.
- DR. NOTTERMAN: It's ironic to hear that a
- drug is a standard of care, but that we can't study
- 14 it so that we can have an appropriate and safe
- delivery mechanism. That's ironic, after all that
- we've worked through.
- DR. SUMMERS: Can I address that, please?
- DR. MURPHY: It does occur. We have
- problems -- we have off-patent products over at NIH
- that we have had multiple meetings about and cannot
- get studied because the whole point of this program
- is you don't know what you don't know, and

- particularly where there are complex cases.
- Now, if you could say with certainty all I
- g care about is -- I'm totally out of my field here --
- all I care about is the white count, then maybe. But
- 5 --
- 6 CHAIRMAN ROSENTHAL: Jeff, please.
- 7 DR. SUMMERS: Neulasta is not the standard
- of care for treating pediatric patients, because it's
- not approved. Neupagin is the standard of care.
- One of the biggest issues for pediatric
- oncology -- I think there are two limiting resources.
- 12 For adult studies the limiting resource is probably
- money. Unfortunately, I think for pediatric oncology
- 14 studies the limiting resource is actually patients.
- The children's oncology group has limited resources
- with regards to patients and with regards to money.
- The priority there, and rightly so, is to study drugs
- that actually have some kind of therapeutic treatment
- effect with regards to the cancer, not necessarily
- 20 supportive care. Even if that supportive care study
- 21 were to help potentially with the practice of
- 22 medicine, that's not where their resources

- necessarily -- so this study was conducted outside of
- $_{\rm 2}$   $\,$  the children's cooperative group, and I think the
- 3 sponsor did the best they could.
- But it's sometimes hard to get the pediatric
- 5 oncology community interested in pursuing studies
- that are supportive care studies.
- 7 CHAIRMAN ROSENTHAL: Thank you.
- Br. Goldstein.
- DR. MURPHY: Just one last. I do want to
- 10 follow up --
- 11 CHAIRMAN ROSENTHAL: Dr. Murphy.
- DR. MURPHY: -- to say that -- I know I'm
- interrupting, but that's a really important point and
- it's something that we just recently dealt with with
- the pediatric oncology subcommittee, where they were
- 16 actually asked which written request they should
- issue, because the COG can only do -- if you're going
- to get a study done in oncology, it's got to be
- through COG. COG basically is the gatekeeper.
- You'll notice that this review says COG has this as
- 21 not a high priority.
- 22 CHAIRMAN ROSENTHAL: That's an important

- 1 point.
- 2 Dr. Goldstein.
- DR. GOLDSTEIN: I just want to follow up on 3 the comments that were just made and point out that our only pediatric oncologist is sitting on the 5 sidelines. I would hate to -- while it may seem 6 obvious what ought to be recommended, I don't want to 7 step on our pediatric oncologist's toes and 8 something that is going to potentially adversely 9 impact their practice or something that they may have 10 better insights into how to deal with than we do. 11
- So if there's a way to -- I don't vote, but 12 my recommendation would be to try to get involvement 13 from the pediatric oncology subcommittee or COG or 14 folks who actually use this drug before 15 something or recommend something that could 16 potentially impact their clinical care. 17
- 18 CHAIRMAN ROSENTHAL: Can we go back to slide 19 number 27, which is the slide with questions.
- 20 (Screen.)
- 21 I'd like to try and simplify some of this.
- 22 It seems like we've ended up at number four.

1	DR. WAGENER: Could I comment on number
2	three?
3	CHAIRMAN ROSENTHAL: Yes, please.
4	DR. WAGENER: I want to comment on this
5	slide also. Let's get back to where we were. This
6	is very similar to the Flovent issue. We have a
7	signal, an AE signal. This one happens to be much
8	simpler because it's a dosing one primarily.
9	Is it possible to add to the label:
10	Warning: Use of the prepackaged syringe has resulted
11	in overdose, period, or overdose in children, period.
12	Something very simple that just simply warns people
13	not to use the prepackaged syringe that way.
14	CHAIRMAN ROSENTHAL: Yes, Dr. Towbin.
15	DR. TOWBIN: I think we ought to go further,
16	because indeed if the delivery system is the problem
17	then forcing people to give the drug through some
18	other mechanism I don't mean the company now, but
19	I mean the provider would remove that.
20	DR. MATHIS: Can I ask just one question of

the division that may help clarify some of this?

CHAIRMAN ROSENTHAL: Particularly if it's a

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- 1 clarifying question.
- DR. MATHIS: Is Neupagin available in a
- 3 multi-dose vial or in a manner that can be dosed
- appropriately for children?
- 5 (No audible response.)
- DR. MATHIS: So Neupagin, which is a lot
- 7 like Neulasta --
- CHAIRMAN ROSENTHAL: I'm sorry, I missed the
- g answer to that question.
- DR. SUMMERS: Yes.
- 11 CHAIRMAN ROSENTHAL: Yes.
- Dr. Mathis, carry on. I didn't mean to
- 13 interrupt you.
- DR. MATHIS: No, no, no. So if there's a
- product that has the same indication and, although
- not labeled for use in pediatrics, has an appropriate
- ability to deliver the right dose to pediatrics,
- perhaps then adding language about this particular
- dosing device not being appropriate for children
- would be helpful, and then people can do with it what
- they need to do with it.
- 22 CHAIRMAN ROSENTHAL: May I ask a question.

1 earlier regarding dosing medication errors inform 2. this discussion? I know it's hard to know without 3

How might the ongoing analyses that were alluded to

- actually having completed the analyses, but give me
- some ideas about how this might inform the process 5
- that we're discussing right now? 6

which would increase that error.

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- DR. ABATE: What I noticed when I 7 looking at the pediatric cases is the wrong-drug 8 errors that are occurring, many of them are between 9 Neupagin and Neulasta. Neupagin is also in a 10 prefilled syringe, which has markings on it. So when 11 we -- I didn't want to go to the recommendation of 12 just put markings on the syringe because then it 13 would make it appear even more similar to Neupagin, 14
- until I can fully go back to 16 beginning of the Neulasta errors, which would be from 17 2002, to get a better picture of the errors that are 18 occurring with Neulasta, I didn't want to make that 19 type of recommendation.
- CHAIRMAN ROSENTHAL: Would it be reasonable 2.1 for us to -- well, I guess there's two questions that 22

- I would ask the committee. One is do we feel like there's enough information to suggest a label change?

  The other is -- and I guess the answer to that is yes, we can go ahead and suggest that change and provide the agency with some of our reflections about what that might include.
- But then the other question is, how should we circle back, when would we like to circle back, yould we like to circle back when the ongoing analyses are completed, and if so might that also result in some labeling changes, and would it be better to wait until all the information is in.
- I don't have a good sense for the answers to those questions, so I just throw them out there.

Dr. Wolfe.

WOLFE: There are some things that we 16 will know a year from now that we aren't going to 17 know, such as the in-depth analysis going back to 18 2002 that Dr. Abate just talked about. But we do 19 know how something that will still be true a year 20 from now, is that the drug is not available in a 2.1 pediatric dosage form because the drug is 22

approved for pediatric use.

2.1

Just to somehow in the label now -- and it

could be accompanied or added later if we find out

more about that -- that part's still going to be the

same. The current dosage form should not be used for

children because it is intended -- it's only intended

for use in adults, and mention at least some of the

errors that have occurred there.

Again, this is a very -- I don't know what the number was before 2006, but 330 patients between 2006 and now and those several errors, and you will likely find more. It's not going to be fewer errors. It will be probably more. And there is -- I don't know the details about the benefits and risks of Neupagin versus this drug, but there is something else available, at least for some people, and there may be, hopefully is, some advantage of this over Neupagin.

But I think that we can at least say now something that raises it to a level higher than the label now does, this dosage form is not for children, period. That does not mean no one can ever use it in

- 1 children. Someone who's willing to pay for this
- whole thing and take a small fraction of the .6 of a
- ml, inject it at the right dose, it doesn't stop
- them. The PK data says in there.
- Anyway, that's my suggestion.
- 6 CHAIRMAN ROSENTHAL: Does anyone want to
- articulate a different opinion, a dissenting opinion?
- DR. SANTANA: Can I offer a comment that may
- g clarify some issues.
- 10 CHAIRMAN ROSENTHAL: Can you --
- DR. SANTANA: It's just a practice comment.
- 12 It has nothing to do with -- maybe the committee can
- understand the difference between the two products.
- 14 That's all I'm contending.
- 15 CHAIRMAN ROSENTHAL: Can I just clarify for
- the record sort of what's going on here in terms so
- that everyone knows how you got to the mike and all
- that. So will you introduce yourself.
- You know, actually I'll ask you the same
- question that I asked before the public hearing,
- which is for speakers to disclose any conflict of
- interest, and if you don't have a conflict of

- interest or don't want to disclose it then you're not
- 2 required to do so before making a statement. But
- 3 this is an opportunity for you to disclose any
- d conflicts of interest.
- DR. SANTANA: My name is Victor Santana.
- 6 I'm a pediatric hematologist-oncologist. My conflict
- is that my institution was involved with both the
- 8 original Neupagin pediatric trials and was also
- 9 involved with the Neulasta pediatric prescription
- trial that you guys have been seeing today.
- In terms of practice, the original product,
- which is called Neupagin, is standard GCSF, and
- that's dosed on a microgram per kilo basis. And
- there are vials. There are different formulations of
- that. So depending on the dose that's calculated for
- the patient, the pharmacy can prepare patient-
- 17 specific doses.
- On average, a patient may -- it's given
- every day, daily. It's not a pegalated product, so
- the original Neupagin is the standard agent that has
- to be given every day until you reach a certain end
- point, which is usually a neutrophil recovery. On an

- average, it takes a pediatric patient between seven and ten days to get there after the chemotherapy is
- administered.
- So the practice is that the pharmacy, if the parent is going to administer the dose at home or the home health agency is going to deliver it at home -- on average, five to seven doses are given to the parent to give at home. That is for the Neupagin, which is the daily administration.
- This agent we're talking about is а 10 pegalated product and it was formulated precisely to 11 avoid the daily administration schedule. So you get 12 one dose and because the kinetics, as was indicated 13 earlier, are receptor-mediated, all you need is one 14 dose until you get to your end point of recovery. 15
- So one of the big advantages of using this in pediatrics, the patients get one shot. They don't get seven to ten shots if they use the alternate product.
- DR. MURPHY: I just want to put on the record --
- 22 CHAIRMAN ROSENTHAL: Yes, Dr. Murphy.

- DR. MURPHY: -- that Dr. Santana was
- 2 speaking as a member of the public because of the
- request of the committee to address a practice issue,
- and he will not vote or be involved in the
- decisionmaking otherwise on this product. So thank
- 6 you.
- 7 CHAIRMAN ROSENTHAL: Thank you.
- Dr. Notterman.
- DR. NOTTERMAN: Can Dr. Santana as a member
- of the public respond to a question regarding
- 11 practice?
- DR. MURPHY: I guess so.
- 13 CHAIRMAN ROSENTHAL: If it will help us to
- move forward. We're running out of time on this
- 15 discussion.
- DR. NOTTERMAN: I have a quick question. I
- think it can even be --
- DR. MURPHY: We also have a member who's a
- pediatric oncologist at the table.
- DR. NOTTERMAN: That'll be fine.
- So were this labeled for use in children and
- were appropriate dosage forms available, taking into

- account the pharmacokinetic information we heard
- 2 would there be a significant use in children,
- 3 pediatric oncology practice?
- DR. SANTANA: I would think so.
- DR. NOTTERMAN: So then I want to ask my
- question again: Why has the agency decided -- and
- 7 maybe you answered it by saying nobody will do the
- studies, and that I guess would be a good response.
- g But why isn't the agency pushing this issue with the
- sponsor, since it might help children? Maybe the
- answer is that they can't get anyone to study it.
- DR. SUMMERS: The sponsor valiantly
- attempted to accrue patients to the study and it took
- them eight years to get to 38 patients. Now, whether
- they could have done that if there were more of a
- 16 financial incentive for them to do or there were
- monetary, civil monetary penalties, that that would
- have made it get done faster -- they did what we
- asked under the pediatric rule when there was the
- 20 pediatric rule.
- The data, after analysis, we felt -- the
- division didn't feel that that could be extrapolated

- to efficacy. I think you have to ask the pediatric
- folks here, colleagues, but under the new biosimilars
- legislation there may be a financial incentive, which
- -- Sandra Quider is the one -- Dr. Quider said one of
- 5 the greatest incentives that we've had to get
- 6 pediatric information on the label was the ability to
- 7 have a written request and give pediatric
- 8 exclusivity.
- 9 With the biosimilars legislation, this
- 10 biologic might be able to fall under that and much
- nore likely to get studies done.
- DR. NOTTERMAN: Thanks very much. That
- 13 clarifies things for me.
- 14 CHAIRMAN ROSENTHAL: Let's go back to the
- question. Now, Dr. Wolfe, will you just reframe your
- suggestion or rephrase your suggestion regarding a
- label change that the agency could consider?
- DR. WOLFE: Well, I think -- you informally
- went around the room and the answer to question one
- is I think people would like some kind of change in
- labeling. Some of it may have to wait for the kinds
- of data that you're looking for now.

But what I was suggesting was to simply say 1 on the label: Because this drug is not approved in 2. children, it is not available in a proper or any 3 pediatric dosage form. The adult dosage form as such should not be used in children. This would prevent a 5 whole syringe from being given. People would still 6 be able to get this pegalated fluid and give it in 7 much smaller doses than the adult dose to children if 8 proper. 9

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So just emphasizing not approved in children, therefore there's no pediatric-specific dosage form available, don't use the adult dosage form, the whole adult dosage form. The whole syringe is the most gross example of that.

CHAIRMAN ROSENTHAL: I'm going to frame another compound question here. So with Dr. Wolfe's articulation of a proposed label change, would the committee feel that such a recommendation is warranted; and in addition to that, that the agency would continue its ongoing efforts to further explore medication errors around the use of this product; and we will also recommend the retention of PK data in

- 1 the label.
- 2 Dr. Notterman, are you voting or do you have
- a question?
- DR. NOTTERMAN: I'm suggesting, and then
- 5 I'll vote.
- 6 CHAIRMAN ROSENTHAL: Okay.
- 7 DR. NOTTERMAN: I wonder if the committee
- 8 would be willing to also advise FDA to consider
- 9 working with the manufacturer to complete further
- studies with respect to efficacy and dosing.
- 11 CHAIRMAN ROSENTHAL: Okay. We heard some
- reasons why that was going to be particularly
- challenging, some of which are outside of the scope
- of the FDA's reach probably, related to COG.
- All right. So I'd like to propose that we
- vote on a recommendation that includes each of those
- four elements: the label suggestions of Dr. Wolfe,
- the encouragement around studies from Dr. Notterman,
- 19 retention of the PK data, and some process that
- 20 involves circling back to the Pediatric Advisory
- 21 Committee after the process of exploring medication
- 22 errors with this medication is completed.

- So all in favor of that four-armed solution?
- 2 (A show of hands.)
- 3 CHAIRMAN ROSENTHAL: Any opposition?
- 4 (A show of hands.)
- CHAIRMAN ROSENTHAL: Any abstentions? We've
- got one, two opposed.
- 7 Any abstentions?
- 8 (No response.)
- CHAIRMAN ROSENTHAL: Let's go around the
- room and vote. Please, I guess if you concur you
- don't need to explain why. But if you are opposed,
- please help us understand your thinking.
- Dr. Wolfe.
- DR. WOLFE: I concur.
- DR. LA RUSSA: Phil La Russa. I concur, but
- maybe what would make it a little clearer is to refer
- to the adult device, rather than the adult
- 18 formulation.
- DR. WAGENER: Jeff Wagener. I disagree. I
- think the first three points I totally agree with,
- but I don't see it's the position of this committee
- in any way, shape, or form to be advising further

- studies on a drug that neither the industry nor the
- $_{\rm 2}$   $\,$  FDA nor COG wants to study.
- DR. NOTTERMAN: Notterman. I concur.
- DR. HOLMES: Greg Holmes. I concur.
- DR. KRISCHER: Jeff Krischer. I concur.
- MS. CELENTO: Amy Celento. I concur.
- 7 DR. RAKOWSKY: Alex Rakowsky. I concur.
- DR. MOTIL: Kathleen Motil. I concur.
- DR. D'ANGIO: Carl D'Angio. I disagree, and 9 I disagree around the issue of trying to discourage 10 the use of the adult device. It's not that I'm 11 against -- it's not that I think the adult device is 12 It's that what we've done is made it a good idea. 13 more difficult for people to use the drug. 14 going to continue to be used and we haven't provided 15 any guidance at all about ways to try to make the 16 device that will continue to be used despite the fact 17 we're going to stamp our feet and say it shouldn't. 18

We haven't done -- we haven't provided any guidance or any suggestion about how to make the device that will continue to be used safer in children, and I think that's the issue.

- DR. SHWAYDER: Tor Shwayder. I agree, but I
  guess I'll do the flip side of your coin and I urge
  the committee to have them have a vial that could be
  drawn up, exactly what you need for the child, based
- 4 arawii ap, enader, what you need for one office, based
- on the PK data.

Thank you.

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adult device in children.

- DR. TOWBIN: Kenneth Towbin. I concur.

  Just making the link very strong between the risk for

  overdose and medication errors and the use of the
- 10 CHAIRMAN ROSENTHAL: Before we go on, I'd
  11 like to thank the people from the agency who have
  12 presented and participated in this discussion, and
  13 also just point out that this is a case in which the
  14 review process seems to have triggered a much more
  15 in-depth undertaking, so I think the process seems to
  16 be working and I applaud your efforts in that regard.
- The next presentation will also be presented by Dr. Karesh. We'll be talking about Prezista.
- 20 And Dr. Santana is back at the table as a 21 voting member of the Pediatric Advisory Committee, 22 and there are no recusals for this product.

1	(Screen.)
2	PREZISTA (DARUNAVIR ETHANOLATE)
3	DR. KARESH: Hello again. This time we're
4	going to discuss darunavir, or Prezista.
5	(Screen.)
6	You are familiar with this outline.
7	(Screen.)
8	Darunavir is a protease inhibitor,
9	originally approved in June 2006. Darunavir is
10	indicated with ritonavir and other anti-retrovirals
11	to treat HIV in patients six years and older.
12	(Screen.)
13	Pediatric dosing is based on body weight.
14	Limitations of use are not to use once daily in
15	pediatric patients; safety and efficacy in patients
16	three to less than six years of age have not been
17	established; and not to use in patients below three
18	years of age.
19	(Screen.)
20	Let us now look at the pediatric study. The
21	general design was that it was a randomized study to
22	evaluate PK, safety, and activity. When interpreting

- the results, please note that all the pediatric
- patients were treatment-experienced.
- 3 (Screen.)
- In this study, the mean CDC4 cell count
- increase was 117 cells per millimeter-cubed. 64
- 6 percent had less than 400 copies per milliliter and
- 50 percent had less than 50 copies per milliliter.
- 8 (Screen.)
- Now let's discuss the safety results. The
- 10 pediatric study showed that the adverse drug
- 11 reactions were comparable to adults and the common
- adverse events were headache, rash, fatigue, or
- 13 related to the GI system.
- 14 (Screen.)
- The grade 3 and 4 laboratory abnormalities
- are shown on this slide.
- 17 (Screen.)
- Since the indication was granted, labeling
- was changed in multiple sections, as seen on this
- 20 slide.
- (Screen.)
- I am now going to highlight some specific

- 1 labeling changes. Labeling provides dosing
- 2 information for patients six years and older and
- 3 states that darunavir should not be used in patients
- less than three years of age due to toxicity and
- 5 mortality observed in juvenile rats. Additionally,
- labeling describes the pediatric study that we just
- discussed.
- 8 (Screen.)
- There are post-marketing requirements to
- obtain additional data in patients three years and
- older. FDA waived the PREA requirement for patients
- less than three years of age because, as noted on the
- previous slide, the juvenile rat toxicology studies
- 14 strongly suggested a safety signal.
- 15 (Screen.)
- Now, turning from labeling to drug use. In
- adults and pediatrics there were approximately
- 18 628,000 dispensed prescriptions and 68,000 unique
- 19 patients.
- 20 (Screen.)
- The pediatric use accounted for less than
- one percent of total prescriptions and patients, and

in zero to three year olds, the age group with the

2 safety signal we discussed, there was a negligible

amount of prescriptions.

4 (Screen.)

Infectious disease was the most common prescribing specialty. Pediatrics was approximately

 $_{7}$  one percent. The top diagnosis code for patients 17

g years of age and older was HIV and specific

infection. The diagnosis codes for pediatrics were

10 not captured.

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11 (Screen.)

Now, with that background, we will discuss

the adverse event reports since approval. There were

36 crude count pediatric reports, which represents

approximately 3 percent of the total number of crude

16 count adverse event reports. As you recall,

pediatrics use accounted for less than 1 percent of

total prescriptions and patients.

19 Please note, the two pediatric fatalities

were in indirect or trans-placental exposures.

(Screen.)

I am now going to show you the breakdown of

- $_{
  m 1}$  the 36 crude count pediatric reports. Of the 36
- 2 crude count pediatric reports, 14 were duplicates;
- and of the remaining 22, 13 were indirect or trans-
- placental exposures. Therefore, there were only nine
- 5 non-duplicated direct exposure reports.
- 6 (Screen.)
- 7 Of the nine non-duplicated direct exposure
- reports, five were labeled adverse events and four
- 9 were unlabeled adverse events.
- 10 (Screen.)
- The 13 in utero exposure cases I mentioned
- showed no pattern of toxicity, and the sponsor
- participates in an active anti-retroviral pregnancy
- 14 registry.
- 15 (Screen.)
- Next we are going to discuss the unlabeled
- adverse events, and then conclude with the labeled
- ones. I know this is a different order than usual,
- but I would like to end with the labeled adverse
- 20 events because the question for the Pediatric
- 21 Advisory Committee concerns two of the labeled
- adverse event cases.

So let's turn our attention to the four unlabeled adverse event cases, which are outlined in the next two slides. You will note that all four

4 patients were on multiple concomitant medications and

there does not appear to be a pattern.

This slide presents the adverse events of cryptococcal and tuberculous meningitis and insomnia and hyperactivity.

(Screen.)

This slide presents the other two unlabeled adverse events, pneumonia-pleural effusion and hypokalemia.

13 (Screen.)

Now to look at the five labeled adverse events. There was one case each of hepatotoxicity and severe skin reaction. There were three reported cases of immune reconstitution syndrome. One was a case in which a patient ultimately developed renal failure. The other two cases were related to autoimmune events. Please note that, although immune reconstitution syndrome is a labeled adverse event, autoimmune is not.

I will discuss these three immune reconstitution cases in a moment. First I want to

3 explain what immune reconstitution syndrome is.

(Screen.)

Immune reconstitution syndrome describes a collection of inflammatory disorders associated with paradoxical clinical deterioration following the initiation of highly active anti-retroviral therapy in HIV-infected individuals despite apparent virologic and immunologic response.

11 (Screen.)

Now, to discuss the three cases of immune 12 reconstitution syndrome. In this first case, a ten 13 year old female on multiple medications developed 14 renal failure. This is counted as a case of immune 15 reconstitution syndrome because it was reported to 16 AERS that way. Please note, renal failure is a 17 labeled adverse event for both tenofovir and 18 etravirine, which this patient was on. 19

20 (Screen.)

21 As I mentioned earlier, two of the three 22 immune reconstitution syndrome cases involved

- autoimmune events. This slide describes a 16 year
- old male with HIV who was diagnosed with ulcerative
- 3 colitis.
- 4 (Screen.)
- 5 This slide describes a 16 year old male who
- 6 developed autoimmune thyroiditis five months after
- 5 beginning darunavir.
- 8 (Screen.)
- So, based on these two autoimmune cases, OSC
- 10 looked further and identified a potential signal
- associating autoimmune problems and anti-retrovirals
- in both adult and pediatric patients. A full review
- of this association in the 27 products in this class
- is under way. We anticipate, based on preliminary
- analysis, several hundred adverse events.
- 16 (Screen.)
- In summary, dosing, efficacy, and safety
- information in patients six years and older is in
- labeling. Limitations of use is in labeling as well.
- The pediatric focused safety review identified nine
- 21 direct exposure pediatric reports, including two
- autoimmune events.

- 1 (Screen.)
- 2 FDA is evaluating autoimmune disorders as a
- 3 potential event for inclusion in the constellation of
- 4 inflammatory adverse reactions known as immune
- reconstitution syndrome, as a class effect associated
- 6 with all HIV drugs. FDA will update the Pediatric
- Advisory Committee once the analysis is complete.
- 8 Does the Pediatric Advisory Committee concur with
- g this approach?
- 10 (Screen.)
- I would like to acknowledge the people
- 12 listed on this slide.
- 13 CHAIRMAN ROSENTHAL: Questions, Dr. La
- 14 Russa?
- DR. LA RUSSA: Are the autoimmune cases all
- U.S. cases or are some of them from the international
- 17 sites?
- DR. KARESH: I would defer to my OSC
- 19 colleague way in the back.
- DR. GISH: The ulcerative colitis was from
- 21 France.
- 22 CHAIRMAN ROSENTHAL: Can you please -- can

- you please introduce yourself?
- DR. GISH: I'm Paula Gish. I'm a safety
- evaluator from OSC, who wrote the review.
- CHAIRMAN ROSENTHAL: Thank you.
- DR. MURPHY: Could the two people at the
- table just identify themselves, please.
- 7 DR. CAO: Kelly Cao, safety evaluator, team
- leader, Division of Pharmacoviligance.
- DR. BELEW: Yodit Belew, medical officer,
- 10 Division of Antiviral Products.
- 11 CHAIRMAN ROSENTHAL: Thank you.
- 12 Hang on just a second. Dr. Notterman --
- DR. GISH: Sorry. The second case was from
- 14 Germany.
- 15 CHAIRMAN ROSENTHAL: Dr. La Russa, did that
- address your question?
- DR. LA RUSSA: Yes. There are extensive
- safety data done in the impact network looking at all
- of these drugs, and I review all of these and I
- 20 haven't seen anything like this from the States. So
- as far as we know there are just these two cases and
- they're both from outside the country.

- 1 CHAIRMAN ROSENTHAL: Dr. D'Angio, then Dr.
- 2 Notterman.
- DR. D'ANGIO: I have a question for somebody
- 4 who I hope knows more about immunology than I do.
- 5 Are these autoimmune phenomenon felt to be something
- that would have happened anyhow and the child now has
- 7 enough -- is immune reconstituted and can now have
- autoimmunity? Or is it felt that these are phenomena
- that result from abnormal immunity when the system is
- reconstituted? Or does no one have any idea?
- CHAIRMAN ROSENTHAL: Dr. La Russa, do you
- 12 have an idea?
- DR. LA RUSSA: Yes. There's probably more
- 14 known about tuberculosis and immune reconstitution.
- 15 I would separate immune reconstitution from
- 16 autoimmune phenomena. Even with immune
- reconstitution syndrome, it's sometimes an artifact
- of the study design rather than actual pathogenesis.
- 19 I'll give you two examples. With TB it's
- very clear that, unless -- in some cases, unless you
- treat the TB first, you're going to see a lot of CD4
- cells come, a hyperinflammatory response, and the

- patient will clinically get worse. Whether you
- actually decide to wait or to start both medications
- at the same time really depends on the status of the
- 4 patient at the time. The current WHO recommendations
- are that you actually start both sets of medications
- if the patient's very ill.
- 7 There was thought to be an immune
- 8 reconstitution syndrome with varicella zoster and
- 9 development of zoster after starting anti-
- 10 retrovirals. But when they actually did the study to
- look at the similar time period just before and just
- after starting anti-retrovirals, it was the same
- 13 incidence at both times.
- To answer your question specifically about
- the autoimmune phenomenon, I think there we really
- don't know a whole lot.
- 17 CHAIRMAN ROSENTHAL: Dr. Notterman.
- DR. NOTTERMAN: Actually, Phil got to my
- 19 question. I was going to ask about separating
- 20 autoimmune phenomenon from the inflammatory
- reconstitution syndrome. I think he addressed that.
- 22 CHAIRMAN ROSENTHAL: Thank you.

1 Dr. Santana.

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DR. SANTANA: My question I think was partly 2 answered from your comment. Combination anti-3 retroviral therapy has been around for a good 10 or 15 years, combination good therapy. So why have we 5 not seen this before? Is it a matter of definition 6 or is it studied like you suggested, that it may be 7 very study-related, and is that going to be a problem 8 as you do your look through different studies looking 9 for this signal? 10

## CHAIRMAN ROSENTHAL: Yes?

DR. LA RUSSA: Autoimmune phenomena have been around for quite a while. The problem that you have is that every time a new drug is added to a regimen you have to readdress the issue to see if there's another signal. In pediatric patients, by the time you get to darunavir you are pretty far along in the course, except for the pretty rare situation where the mother transmits highly resistant virus to the kid, and you may have to start with something that's not a first-line regimen.

So we look at all these, but you may end up

- with a patient whose on five drugs and then develops
- this, and then you have to figure out whether it's
- 3 this drug or it was going to happen or whether it was
- $_{4}$  the combination.
- 5 CHAIRMAN ROSENTHAL: All right.
- Yes, please.
- DR. BELEW: Just to echo Dr. La Russa's 7 point, all HIV drugs do have that class labeling for 8 immune reconstitution syndrome. But in the label 9 it's specific to infection-related because that's 10 pretty much what has been seen during clinical 11 trials. But if you go into the literature you would 12 see reports of autoimmune being one of the possible 13 manifestations of immune reconstitution syndrome, 14 which is essentially what we're doing now is looking 15 at post-marketing errors reports and trying to figure 16 there's a true association between HART if out 17 regimens and autoimmune disorders. 18
- As already mentioned, because they're on multiple drugs it's very difficult to pinpoint it to one drug because they are on at least three drug regimens.

- 1 CHAIRMAN ROSENTHAL: So I guess the question 2 for the committee then is, the way that this is 3 framed -- just to be clear about what the approach 4 is, the approach is to continue evaluation of 5 autoimmune adverse events, looking across the class.
- Is that -- am I understanding -- yes, please help me. Help me clarify.
- DR. CAO: We noted in this pediatric review that there were two cases of autoimmune diseases and we are actually -- we've already started looking at a more thorough review looking at all anti-retrovirals and autoimmune diseases. That's already under way.

However, I do want to point out that immune 13 reconstitution syndrome, it's noted in the literature 14 it's a spectrum of inflammatory diseases. 15 well known is the infectious disease portion, but it 16 does include autoimmune diseases and 17 inflammatory disorders. did So when we the 18 preliminary look into all patient populations, 19 including adults, in all anti-retrovirals, we did 20 find many other autoimmune disease -- reports of many 21 other autoimmune diseases coming up. 2.2

We think it may fit into that spectrum of 1 autoimmune reconstitution syndrome. So that's where 2. we are right now with this.

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- CHAIRMAN ROSENTHAL: Can you clarify what time frame the analysis is likely to be -- over what 5 time frame it's likely to be completed? In other 6 words, one of the things that you're kindly offering 7 is to circle back to the Pediatric Advisory Committee 8 when the analyses are complete. When might we expect 9 that? 10
- DR. CAO: At this point it probably will be 11 completed maybe around the first quarter to second 12 quarter of next year. 13
- CHAIRMAN ROSENTHAL: Okay, so maybe as early 14 as our next meeting? 15
- DR. CAO: Possibly. More likely the second 16 quarter, the end of the second quarter. 17
- That's when they complete it. DR. MURPHY: 18 They then have to give it to us and we have to pull 19 the division in and we have to have a discussion and 20 put together a review.
- CHAIRMAN ROSENTHAL: Dr. Murphy, I don't 22

- think I've ever seen you move that quickly trying to reach for the button on the microphone.
- Other questions or issues? Yes, Dr. La Russa.
- I will just say that a lot of DR. LA RUSSA: 5 people would probably disagree with the sort of large 6 wastebasket approach looking to at 7 reconstitution syndrome. I think it probably happens 8 that with tuberculosis in certain situations when the 9 microbial load is extraordinarily high. The evidence 10 is pretty good for cryptococcal meningitis. 11
- 12 For everything else, I think it's really up
  13 in the air whether there really is a signal. The
  14 right approach to do is a self-controlled series.
  15 What most of the studies have looked at is we start
  16 the drug today and what happens in the six weeks to
  17 three months after, and that really I think gives you
  18 the wrong idea about what actually is going on.
- CHAIRMAN ROSENTHAL: So can we suggest that
  while you're doing these analyses you consider both
  the narrow and the broad definitions of immune
  reconstitution and autoimmune outcomes.

- DR. BELEW: The issue with that is it's not
- unique to darunavir. It's a class labeling effect,
- so we can't just do that for darunavir only and not
- do it for the rest of the anti-retroviral drugs.
- 5 CHAIRMAN ROSENTHAL: My understanding was
- that that was the proposal, that you were going to be
- 7 looking across the class.
- DR. BELEW: Correct. But until the review
- by the OSC division is completed, we won't be able to
- 10 make any labeling change.
- CHAIRMAN ROSENTHAL: Oh, yes, I don't think
- we're recommending a labeling change. I think we're
- just -- I think we're trying to agree with your
- 14 approach.
- So let's take a vote -- I'm sorry. Dr.
- 16 D'Angio. DR. D'ANGIO: Just one
- 17 question for the agency. It sounds as if no one
- right now is recommending a labeling change, but the
- initial safety report recommends a labeling change.
- 20 Could someone help me understand the thinking that
- led to the current question for us?
- DR. MURPHY: I hope I get this correct. My

understanding is we got the review and then we got
everybody back, because we were looking at just this
product, because the review comes to everybody, then
we all have to discuss it. We actually had similar
discussions as to whether it was reconstitution or
autoimmune, other drugs that might be doing this, and

that's why now it's a bigger issue.

- But one of the things that would be very good for the committee to always do is look at what the recommendation is in the OSC review. If you see that we have a different question, you might want to know why.
- DR. CAO: I think we felt we needed further
  characterization other than just these two cases,
  because there are so many diseases. We needed to
  know more about the time to onset. It's a different
  phenomenon than the infectious virus.
- DR. D'ANGIO: I agree with you. It just helps me to understand how the thinking went.

  Thanks.
- DR. MURPHY: It's the timing of the process, basically.

CHAIRMAN ROSENTHAL: All right. Well, I 1 think the committee is generally supportive of your 2. work in this area. So perhaps we can vote on the 3 question and affirm that for you. So all in favor of 4 continuing with the approach as it's been outlined? 5 (A show of hands.) б CHAIRMAN ROSENTHAL: Thank you. Any 7 opposed? 8 (No response.) 9 CHAIRMAN ROSENTHAL: Any abstentions? 10 (No response.) 11 CHAIRMAN ROSENTHAL: So there's a unanimous 12 vote. Dr. Wolfe, will you start. 13 DR. WOLFE: Sid Wolfe. I support the vote. 14 DR. LA RUSSA: Phil La Russa. I agree. 15 DR. WAGENER: Jeff Wagener. I agree. 16 DR. NOTTERMAN: Dan Notterman. I agree. 17 DR. HOLMES: Greg Holmes. I agree. 18 DR. KRISCHER: Jeff Krischer. I agree. 19 MS. CELENTO: Amy Celento, concur. 20 DR. SANTANA: Victor Santana. I agree. 2.1

DR. RAKOWSKY: Alex Rakowsky, agree.

- DR. MOTIL: Kathleen Motil, concur.
- DR. D'ANGIO: Carl D'Angio, concur.
- DR. SHWAYDER: Tor Shwayder, concur.
- DR. TOWBIN: Kenneth Towbin. I agree.
- CHAIRMAN ROSENTHAL: All right. Thank you
- 6 very much.
- 7 It's time for a break. We need to return
- exactly at quarter to 4:00 to start the next session.
- We will be having people calling in, or at least one
- 10 person calling in for the next discussion. So we
- need to try and be on time for that. So 12 minutes.
- 12 Thank you.
- 13 (Recess from 3:32 p.m. to 3:48 p.m.)
- 14 CHAIRMAN ROSENTHAL: We're going to get
- started here for the home stretch. We've got four
- 16 products to discuss. I was wrong about someone
- 17 calling in for this discussion because another
- arrangement was made, so we no longer have to rely on
- the conference calling system.
- For the next product that will be discussed,
- again Dr. Karesh will be helping us find our way
- through this, and we'll be talking about Pegintron.

1	DI. Nocceiman is recused from chis discussion.		
2	(Screen.)		
3	PEDIATRIC FOCUSED SAFETY REVIEW		
4	PEGINTERFERON ALFA-2b (PEGINTRON)		
5	DR. KARESH: Hello, again. My final talk		
6	today will be about peginterferon alfa-2b or		
7	Pegintron.		
8	(Screen.)		
9	You are familiar with this outline.		
10	(Screen.)		
11	Peginterferon alfa-2b, or Pegintron, is an		
12	inducer of innate antiviral immune response, and was		
13	originally approved January 2001. Pegintron is now		
14	approved in combination with ribovirin for chronic		
15	hepatitis C in patients three years and older and as		
16	monotherapy in adults.		
17	(Screen.)		
18	For pediatric patients, Pegintron is		
19	administered in combination with Rebetol. Pegintron		
20	is dosed by body surface area and Rebetol by body		
21	weight.		

(Screen.)

- The next four slides list the warnings and 1 precautions contained in Pegintron's labeling. These 2. include birth defects, fetal deaths, and hemolytic 3 anemia with ribavirin. Neuropsychiatric, cardiovascular, endocrine, and ophthalmologic 5 problems are described as well and are listed on this 6 slide. 7
- 8 (Screen.)
- 9 Cerebrovascular, bone marrow, autoimmune, 10 gastrointestinal, and pulmonary problems are listed 11 on this slide.
- 12 (Screen.)
- Liver, renal, dermatologic, dental, and gastrointestinal problems are listed here.
- 15 (Screen.)
- Finally, with the pediatric submission, an additional warning and precaution regarding weight loss and growth inhibition was added.
- 19 (Screen.)
- Now that we have discussed the background information, we are going to talk about the pediatric study, which assessed safety, efficacy, tolerability,

- and PK of Pegintron and Rebetol. Depending on their
- viral load and genotype, patients received Pegintron
- for up to 48 weeks.
- 4 (Screen.)
- 5 Treatment duration for the specific
- 6 genotypes is presented on this slide.
- 7 (Screen.)
- As you can see, the efficacy end point was
- $_{\rm 9}$   $\,$  defined as undetectable hepatitis C virus RNA at 24  $\,$
- 10 weeks.
- 11 (Screen.)
- This slide shows the sustained virologic
- response of 107 patients, depending on genotype. The
- 14 24-week response is presented in the middle column
- and the 48-week response is on the right.
- 16 (Screen.)
- Now to discuss the safety results of the
- pediatric study. Of the 107 pediatric patients,
- there were no fatalities or life-threatening adverse
- 20 events. There were three non-fatal serious adverse
- events.
- 22 (Screen.)

Of the three non-fatal serious adverse

 $_{\rm 2}$   $\,$  events, only one occurred while the patient was on

therapy. A 12 year old male fell off his bike.

4 (Screen.)

The pediatric study revealed important psychiatric, endocrine, and growth information. I would like to call your attention to the growth problems.

g (Screen.)

Labeling explains that the weight and height
gain of pediatric patients lags behind that predicted
by normative pediatric data. Additionally, severely
inhibited growth velocity was observed in 70 percent
of patients while on treatment, and of these 20
percent had continued inhibited growth after 6 months
of follow-up.

(Screen.)

17

Overall, in the pediatric study the adverse 18 reaction profile was similar to adults, and 19 majority of the adverse reactions were mild 20 moderate in severity. Severe adverse reactions 21 occurred in 7 percent of patients, and the most 22

- prevalent adverse reactions are listed on this slide.
- 2 (Screen.)
- Looking at the laboratory abnormalities, 3 most changes were mild or moderate. Decreases in 4 hemoglobin, white blood cells, platelets, 5 neutrophils require dose reduction may or 6
- 8 (Screen.)

7

discontinuation from therapy.

- The efficacy and safety results I just talked to you about are reflected in labeling.
- 11 (Screen.)
- Now we are going to switch gears and discuss

  Pegintron use and then adverse events. Between

  August 2008 and July 2010, pediatric patients

  accounted for approximately 1 percent of the patients

  receiving Pegintron.
- 17 (Screen.)
- Looking who prescribes at Pegintron, 18 gastroenterologists are most common, while pediatric 19 providers account for less than one percent. The top 20 diagnosis code corresponds to the approved 21 indication, hepatitis C treatment. Diagnosis codes 22

- for pediatrics were not captured.
- 2 (Screen.)
- we will discuss the adverse 3 reports. There were 58 pediatric crude 4 reports, which is less than one percent of the total 5 number of AERS reports. This parallels the Pegintron 6 use we've discussed. Please note that of the three 7 crude count pediatric death reports, one was miscoded 8 and the other two were transplacental cases. 9
- 10 (Screen.)
- This slide breaks down the 58 pediatric crude count AERS reports. We are going to discuss the 19 serious pediatric direct exposure non-duplicated cases in detail.
- 15 (Screen.)
- In 7 of the 19 pediatric serious adverse events, Pegintron was used for hepatitis C treatment, which is the only approved indication. The other 12 uses were for non-approved indications, including cancer and hepatitis B treatment.
- 21 (Screen.)
- 22 As I mentioned earlier, none of the

pediatric serious adverse events due to direct exposure were fatal.

3 (Screen.)

I'm going to present the adverse events in order of frequency and will draw your attention to the unlabeled adverse events as we go through them.

Please pay particular attention to the five hepatic cases we are going to start with.

There were five hepatic cases, two of which
were possible liver transplant rejections. The
details of these two possible liver transplant
rejection cases are presented on this slide.

Please keep these two cases in mind as we will come back to them.

15 (Screen.)

Pegintron labeling states that Pegintron has
not been studied for the treatment of hepatitis B in
liver or other organ transplant recipients. Of the
five hepatic cases, two involve elevated liver
function tests. The Labeling outlines the need for
hepatic function monitoring.

22 (Screen.)

There was one case of autoimmune hepatitis 1 and there is a box warning that Pegintron may cause 2. autoimmune disorders.

(Screen.) 4

3

four cardiovascular were 5 events which are labeled. Three of the cases 6 involved cardiomyopathy and involved one 7 hypertension. 8

(Screen.) 9

There were three rheumatology adverse events 10 cases, which are unlabeled. The cases are presented 11 on this slide. The first patient listed was on 12 chemotherapy for osteosarcoma and she developed knee 13 swelling at her endoprosthesis site. 14

The second patient listed was diagnosed with 15 septic arthritis and prosthetic infection associated 16 with a central line infection. 17

The third patient, a nine year old with 18 melanoma, had positive rechallenges to Pegintron. 19

(Screen.) 20

There were three CNS adverse events, which 2.1 are labeled. Two involved hearing loss and one 2.2

involved myoclonic jerks in a patient with 1

neurofibromatosis. 2.

(Screen.) 3

One case involved glucose intolerance, which 4 is a labeled adverse event.

(Screen.) б

5

The final 3 of the 19 cases are presented on 7 this slide. One case involved nephrotic syndrome, 8 which is a labeled adverse event. There was one case 9 each of cutaneous emboli and mitochondrial toxicity, 10 which are unlabeled adverse events. 11

(Screen.) 12

You may recall I asked you to pay particular 13 attention to the two liver transplant rejection 14 The reason is that FDA has identified cases. 15 liver transplant rejection cases with possible 16 another Pegintron product as well, and FDA 17 considering class labeling regarding adult and 18 pediatric liver transplant rejection. 19

(Screen.) 20

So, in summary, information from pediatric 21 studies is incorporated into labeling and FDA is 2.2

- 1 considering class labeling regarding liver transplant
- 2 rejection in both adult and pediatric patients. Does
- 3 the Pediatric Advisory Committee concur or have any
- 4 recommendations?
- 5 (Screen.)
- I'd like to acknowledge the people are
- 7 listed on this slide.
- 8 CHAIRMAN ROSENTHAL: Thank you.
- g Dr. Wolfe.
- DR. WOLFE: From your third last slide, you
- said you've discovered liver transplant rejection or
- possible in another interferon product. What is the
- product and what are the data on that product?
- DR. KARESH: Let me refer to division to see
- what they say.
- DR. BELEW: It's actually under review.
- 17 It's new information that we received from another
- sponsor of interferon, and the division is currently
- 19 reviewing that information.
- DR. WOLFE: You're considering class
- labeling, so it must be a little more information
- than it's just currently under review, because it's

- in the slide as -- can you just give us a little bit
- of a clue, even if it isn't definitive? More than
- 3 one case? What?
- 4 (Pause.)
- CHAIRMAN ROSENTHAL: You know how the
- 6 Pediatric Advisory Committee is. If you give us a
- little thread, we'll see what we can get out of you.
- To Dr. Wolfe's point, some of our ability to
- make a decision about whether we concur with the plan
- as outlined sort of depends on knowing a little
- something about it. But we could always change the
- question in some way if you're really not able to
- talk to us about what you've got.
- DR. BELEW: I can at least give you some
- background. As the OSC was reviewing the pediatric
- 16 data, they identified transplant rejection in
- pediatric cases, one or two. At that time, they came
- to the division to discuss that case. As that was
- happening, the division also received a supplement
- from a different interferon and that supplement also
- has information about potential transplant rejection.
- Now, that part of the review process is the

- part that I said I'm not sure if I can go into it
- because it's just been received and being reviewed.
- 3 But we will give you some information about the AERS
- $_{
  m 4}$  data that we had received that led to the
- 5 identification of rejection.
- DR. WOLFE: Can you just tell us if it's
- more than one case from the other product?
- DR. BELEW: Yes, it's more than one case.
- GHAIRMAN ROSENTHAL: Dr. D'Angio and then
- 10 Dr. Santana.
- DR. D'ANGIO: This is just so that I can
- understand a little bit better. What's the proposed
- 13 -- does anyone know what the proposed mechanism of
- 14 action of peginterferon that would lead to an
- enhanced immune response, that would in turn lead to
- 16 transplant rejection? Does anybody know the
- mechanism of action?
- CHAIRMAN ROSENTHAL: Dr. Rakowsky, would you
- 19 like to?
- DR. RAKOWSKY: Actually, in the review --
- 21 I'm blanking on which page it was, but towards the
- end of the review there was the theory that as the

- 1 hepatitis C load is decreased you have more
- 2 inflammation, leading to more inflammation of the
- actual liver. Whoever wrote the safety review
- actually had a very nice summary of that on one of
- 5 the pages.
- 6 CHAIRMAN ROSENTHAL: Dr. Motil had to excuse
- herself from the meeting to make a flight. But she
- left me a statement to read, and this may shed some
- g light on things as well. Dr. Motil says, quote:
- "It is difficult to infer causality between
- the use of interferon alpha-2 and liver transplant
- rejection, because the treatment of hepatitis C with
- 13 interferon depends on the simultaneous reduction of
- immunosuppressive therapy. If hepatitis C recurs
- despite liver transplantation, the pathological end
- 16 point, which is the liver biopsy, does not
- 17 differentiate between hepatitis C and liver
- 18 rejection."
- That's all -- oh, and Dr. Rakowsky, if you'd
- 20 like to.
- DR. RAKOWSKY: This is page 10 of the review
- from the FDA that's under discussion, on the second

- paragraph. It says: "Fernandez et al." -- and 1 there's a reference for liver transplantation --2. "discuss a potential hypothesis as to why alpha 3 interferon therapy may lead to liver transplant 4 rejection. As the therapy leads to hepatitis C 5 and improvement in liver efficiency, clearance 6 reduced trough levels of immunosuppressive drugs may 7 This increased metabolism of these agents may occur. 8 lead to improved hepatic microsomal function through 9 HSV clearance. As a result, liver transplant 10 rejection occur indirectly due may to alpha 11 interferon therapy." 12
- 13 CHAIRMAN ROSENTHAL: Thank you. I actually
  14 read that last night and I guess I was a little bit
  15 closer to rapid eye movement sleep than I thought.
- Dr. Santana.
- DR. SANTANA: Is this an issue with interferon alpha-2b or with the pegalated interferon alpha-2b? Can you share that with us?
- VOICE: We did a review in AERS looking at all alpha interferon products and found cases, representative cases in the adult population, for all

- the products, including Pegasis, Pegintron, and
- 2 Intron A. We did not have any representative cases
- 3 using -- with Intragin use. We attribute that to
- 4 possible load drug use of Intragin for a potential
- reason as to why we may not have found any cases with
- 6 Intragin in AERS.
- 7 CHAIRMAN ROSENTHAL: Dr. Shwayder.
- DR. SHWAYDER: I have to ask a question out
- of ignorance. These are people who've lost their
- liver function due to hepatitis C and then have been
- transplanted, and the hepatitis C is still in their
- body, so it re-infects the transplanted liver? Am I
- right about this? As a baseball fan, it's like
- leaning into a curve ball. Can you explain?
- 15 VOICE: In the pediatric patient population,
- the reason for transplant may be different other than
- 17 hepatitis C. In our representative cases with
- Pegintron, the patient had a transplant due to bile
- 19 duct atresia. The adult population may be more
- likely to have transplants due to hep C or other.
- DR. SHWAYDER: So they just get hep C right
- 22 back again, so it just extends their life a few years

- before it shuts down the second liver?
- 2 VOICE: Most patients who are transplanted
- 3 with -- most adult patients who are transplanted go
- on to develop a recurrence of hep C and require
- 5 treatment.
- DR. SHWAYDER: Okay. Marvelous world.
- 7 CHAIRMAN ROSENTHAL: Other? Yes, Dr.
- 8 Wagener.
- DR. WAGNER: So I just had one question.
- One other serious adverse event which is unlabeled is
- the third case you have, that is on page 30. A nine
- 12 year old female who was treated with melanoma
- developed infusion and then redeveloped infusion with
- 14 reexposure. Are you not considering that possibly
- related to the drug, or is it just not in the
- 16 frequency that you feel should also be included in
- the label, that there may be rheumatologic effects?
- DR. KARESH: I think the latter, but I defer
- 19 to OSC.
- DR. CAO: I believe the case that you're
- 21 referring to, the indication for use was for
- osteosarcoma. That is not a labeled indication.

- 1 That case I believe was from a clinical trial study,
- and so we really refrain from making any labeling
- 3 recommendations based on that.
- DR. SANTANA: Can I add to that?
- 5 CHAIRMAN ROSENTHAL: Yes, please.
- DR. SANTANA: There are two national
- 7 pediatric oncology trials that are using pegylated
- 8 interferon. One is for osteosarcoma, which is a
- g randomized trial between Europe and the U.S. So
- there is going to be a lot of signals there, because
- there's going to be -- I think the target number of
- patients is in the hundreds.
- Then there is a pegylated interferon for the
- 14 treatment of childhood melanoma, which is a rare
- condition, but it's one study and hopefully it'll
- capture most of the patients. So that's why you're
- beginning to see these signals in pediatric cancer,
- 18 because there are two trials that are ongoing
- 19 currently. It's not off-label use. It's within a
- 20 clinical trial.
- DR. MURPHY: Let me ask OSC. I think the
- case he was referring to was a nine year old with a

- melanoma, that had the rechallenge. I think that's
- what your question is.
- 3 CHAIRMAN ROSENTHAL: Yes, this patient on
- $_{4}$  the bottom of this slide.
- DR. MURPHY: Yes, slide 30, page 5.
- If we're not considering that for some
- reason, is it just because it's one case and you're
- not ready to say that that's something you want to
- 9 put in the label?
- DR. CAO: Sometimes that is the case,
- although with that one, because it was a positive
- rechallenge, it's something that we can consider
- putting it into the label. At this point, I think we
- 14 really steered away from making recommendations
- because that was likely to be part of a clinical
- trial, and when the sponsor comes in seeking a new
- 17 indication the safety from the trials would be
- evaluated at that point and all the safety data would
- be incorporated into the labeling.
- I think that's kind of why we had held off
- on that. But that's up for discussion if the
- committee feels that that is something that would be

- valuable to include in the labeling at this point.
- 2 CHAIRMAN ROSENTHAL: Dr. La Russa.
- DR. LA RUSSA: Do you have any more details
- about the mitochondrial toxicity case five hours
- after getting a dose? How was the diagnosis made?
- DR. KARESH: I don't have any further
- 7 details.
- VOICE: All of the details that were
- 9 provided to us are listed in this review.
- Unfortunately, we don't get -- typically don't get a
- 11 lot of data.
- 12 CHAIRMAN ROSENTHAL: So can I make sure that
- 13 I'm understanding what's going on at the agency now
- in terms of this issue. One, there is -
- consideration is being given for whether some class
- 16 effect statement should be used regarding the
- potential relationship between Pegintron alfa-2b and
- 18 similar agents and liver transplant rejection.
- 19 That's part one.
- 20 Part two is that that determination is going
- 21 to come from an evaluative process that's just
- getting started, based on very recently obtained

information. Is that right?

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DR. BELEW: That's correct.

CHAIRMAN ROSENTHAL: And it sounds like it's 3 that, regarding say the suffusion perhaps some other -- the effusion I guess is the 5 only unlabeled signal that's come up, new signal 6 that's come up. But your approach to that is going 7 to be to wait and see how the dust settles. I don't 8 mean that in a way that implies passivity on the part 9 of the agency, but once the agency goes through this 10 evaluative process then things like the unlabeled 11 finding of the effusion might then be incorporated 12 into a more comprehensive approach to label changes; 13 is that right? 14

DR. CAO: We continually monitor adverse event reports that come in. So if we receive another report of effusion, we may then at that point decide to do labeling. But at this point with a single report, even though it seems like it's a good case with a positive rechallenge, we just haven't made the recommendation to put that in the labeling, but we would continue to monitor for additional reports.

- CHAIRMAN ROSENTHAL: So can you help us to 1 understand the thinking around this decisionmaking 2. I'm understanding that an effusion, even process? 3 with this retest recurrence, reexposure recurrence, doesn't quite meet some threshold. Clearly, 5 someone died then that would meet the threshold. So 6 where do you draw the line in terms of how do you 7 make this decision, so that we better understand the 8 processes within the agency? 9
- DR. MURPHY: I do think timing has something to do with it, because sometimes the committee makes a recommendation and the division doesn't always take it for labeling because they know that -- well, one, they just may disagree scientifically. They will discuss it, but may disagree on the evidence.
  - But the second is sometimes they know they're going to be doing more labeling, and so instead of making a recommendation -- but I guess your question is, irrespective, would you have made it. I think they're saying maybe, maybe not. Yes.

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CHAIRMAN ROSENTHAL: So my first question was I think closer to what you were just

- articulating, Dr. Murphy, which is -- but my second
- $_{\rm 2}$   $\,$   $\,$  question was where is the threshold for acting as the
- new information is coming in.
- Yes, Dr. McMahon?
- DR. McMAHON: I guess I can take a crack at
- it. I think it's not all that usual that we put a
- single case in the label. I'm not saying it's never
- happened, but it seems -- and there's not any -- to
- g answer your question, there's not any one threshold
- 10 that a case would have to cross. That's not
- something that's in the rule book or something.
- But a case would have to be extremely
- 13 convincing in and of itself and be extremely serious
- both, I think.
- 15 CHAIRMAN ROSENTHAL: Okay. So the answer is
- that this decision is made in the context of the
- indication of the adverse event and with the totality
- of information. Fair enough. So for this particular
- product, we're not considering doing anything with
- the effusion complication, although we are continuing
- our surveillance for things that might be related to
- 22 that.

- 1 All right. Other --
- DR. MURPHY: Again, Geof, that's our
- 3 recommendation, yes. So you can make any
- 4 recommendation you would like.
- 5 CHAIRMAN ROSENTHAL: So I was going to ask,
- are there other opinions about what should be done or
- how this should be approached? Yes, Dr. Rakowsky.
- DR. RAKOWSKY: Considering we have
- 9 melanoma study opened by COG and -- do children with
- 10 melanoma get effusions commonly? I've got my
- oncology buddy next to me.
- DR. SANTANA: No. Well, first of all,
- 13 interferons are not widely used in pediatric
- oncology, so let's start from there. So we don't
- have a lot of data for the use of this product in
- 16 pediatric oncology, and there's not a lot of off-
- label use either because nobody knows where to use it
- 18 anyway.
- So what I was alluding to is that there's
- two ongoing studies that I think will help us define
- 21 better what the toxicity profile of this particular
- 22 class of drugs will be in pediatric oncology

- 1 patients.
- I'm not saying that we should hold until 2 those studies are mature or give us data to make a 3 recommendation about a specific event, because I think, like you suggested, each event is judged 5 individually based on its severity and so on and so 6 forth, and you will be getting those reports through 7 those studies as they're being conducted. And at the 8 end you will also get the full safety report. 9
- So personally, related to this patient, to 10 me it hasn't crossed a threshold that I would advise 11 the agency to do anything with the label in terms of 12 effusion. But clearly you have a program that you're 13 looking into it as the case reports are coming 14 through, particularly through those clinical trials 15 that are being done, and then you can make a decision 16 later on. 17
- 18 Is that fair?
- 19 CHAIRMAN ROSENTHAL: It sounds fair. Are 20 there other opinions on this?
- (No response.)
- 22 CHAIRMAN ROSENTHAL: So does the committee

- concur with the current plan, which is to consider
- 2 this class labeling issue and to look at new data as
- it comes in? Yes, Dr. Wagener.
- DR. WAGENER: Just a clarification. Again,
- 5 in the original information we were given it says
- 6 that they were proposing that for this specific
- 7 product there would be a new labeling requirement
- having to do with transplant. My understanding is
- they're still going to do that, and then in addition
- to that they're looking the a class effect, or are
- 11 you not going to do what was in that original
- statement and just do a class effect?
- 13 CHAIRMAN ROSENTHAL: It seems like --
- DR. MURPHY: I think it was the OSE
- recommendation at that time. But again, looking down
- to OSE to make sure I'm saying this correctly, at the
- time of this individual product review, that was the
- 18 recommendation. But right now, after internal
- discussion, that's the recommendation.
- Now, you can disagree with it and say you
- like the first one better. That's fine, but right
- now this is where we are.

1	CHAIRMAN	ROSENTHAL:	Yes?

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DR. WAGENER: So just a clarification. 2 You've identified adverse events related to this 3 specific product and I'm not sure why not to put this in, as originally proposed, and then a year down the 5 road or however long it takes just look at it as a 6 class effect. Because there has been an identified 7 issue with this specific one. 8

So does it have to do with cost of doing that, or what takes one off the market and onto a different approach?

DR. CAO: Well, we -- OSE had made the recommendation to add liver transplant rejection for this particular product based on this pediatric review. And after having discussions with the review division, we're all on board, and I think at this point the reviews may not be finalized, but I think we have enough of it that I think it is going in the direction that there's going to be a class labeling change where all of the peginterferon -- all the interferon products will have this type of labeling.

22 CHAIRMAN ROSENTHAL: So maybe what you're

- hearing from the committee is that there is the sense
- that there should at least be that comment in the
- 3 label for this particular product, and then if you
- get to the point where it's a class effect then you
- 5 can handle it that way.
- Yes, Dr. La Russa?
- 7 DR. LA RUSSA: Just remind us, how much time
- do you think you need to complete your class review?
- 9 VOICE: We've taken a look at the other
- alpha interferon products already and have submitted
- a memo within the agency that identified that other
- cases with Intron A have been noted, but we didn't
- know any cases with Introgen. Then with the other
- peginterferon products, there's data in house already
- 15 to suggest potential cases of liver transplant
- rejection with that peginterferon product.
- DR. LA RUSSA: So we're talking about weeks?
- Weeks, months, a year? Is that the issue?
- DR. MURPHY: Yes. As I said, timing is
- 20 sometimes -- is often the issue here, because we get
- information, we start additional research, and then
- 22 we don't want to delay forever coming to the

committee, so we come to the committee in an incomplete state.

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But what you're hearing is that it's a high probability that there will being labeling. What we could say -- you could answer this by saying, yes, we think there should be, and if you don't do it in a certain period of time we want you to come back and tell us why you haven't done it. I mean, you could do that if you're worried that we won't get it done.

CHAIRMAN ROSENTHAL: You know, I'd just like to follow up with what you're saying, Dr. Murphy, and speak to the fact it does feel, on the committee, feel like the process is working. For many years on the committee there have been requests of the agency that information be brought to us as expediently as possible even if there was uncertainty in the data. I think these types of discussions will arise just because the agency's been responsive to that request.

So I actually want to just go on record as saying that I appreciate the responsiveness of the agency to bring these things to the committee early, and that I think the committee can tolerate a little

- bit of uncertainty in some of this going forward.
- Now, was there a question over my shoulder?
- Yes, Dr. Rakowsky and then Ms. Celento.
- DR. RAKOWSKY: Is there any harm to doing a
- 5 label in an individual product before -- knowing that
- you may do a class label a year down the road? Does
- 7 that box you into specific wording in a class label
- because you've already kind of set the precedent with
- 9 one product?
- DR. BELEW: I can speak in general terms.
- If we anticipate that there is going to be a class
- label, I think it's just more streamlined to do all
- the labeling together and make the wording consistent
- across all the different drugs, as opposed to having
- a specific label for this one and the rest of the
- 16 class different.
- DR. MURPHY: We have actually worded this
- differently, because what you don't want to do is
- drive somebody from one product to another because
- they think the other product's safer, when really
- it's not. So we've done this a couple times with
- this committee previously, where we were halfway

- through the -- we'd done the methylphenidates and we hadn't done the amphetamines, and so we said: Please
- don't make us do a relabeling change for the
- 4 methylphenidates until we get through with the
- 5 amphetamines, to make sure they don't have the same
- 6 thing.
- 7 So we didn't word it that way, but
- fundamentally what we're saying is, do you -- it
- 9 sounds like you think we should make the labeling
- 10 change, and are you willing to wait until we finish
- looking at it for the class?
- 12 CHAIRMAN ROSENTHAL: Let me ask the
- 13 committee: Would people be willing to wait for some
- not undefined period of time while the agency works
- through this class effect issue? Then would the
- agency be willing to circle back with the committee
- at some point perhaps in the six-month period or so
- to tell us how things are going?
- DR. BELEW: I think that's a pretty
- reasonable approach. We can definitely provide you
- with an update or maybe even the process of labeling
- changes with the next session.

- 1 CHAIRMAN ROSENTHAL: So I've just outlined a
  2 plan. Does the advisory committee concur with the
  3 plan as outlined? All in favor?
- (A show of hands.)
- 5 CHAIRMAN ROSENTHAL: Any opposed?
- 6 (No response.)
- 7 CHAIRMAN ROSENTHAL: And any abstentions?
- 8 (No response.)
- 9 CHAIRMAN ROSENTHAL: So it's unanimous
- support for this, for the plan as articulated. Thank
- 11 you very much.
- Actually, let's go around and do the vote to
- the record. Dr. Wolfe, please.
- DR. WOLFE: Sid Wolfe, yes.
- DR. LA RUSSA: La Russa, yes.
- DR. WAGENER: Wagener, I agree.
- DR. HOLMES: Greg Holmes. I agree.
- DR. KRISCHER: Jeff Krischer. I agree.
- MS. CELENTO: Amy Celento, concur.
- DR. SANTANA: Victor Santana. I agree.
- DR. RAKOWSKY: Alex Rakowsky, concur.
- DR. D'ANGIO: Carl D'Angio, concur.

DR. SHWAYDER: Tor Shwayder, concur. 1 DR. TOWBIN: Kenneth Towbin, agree. 2 CHAIRMAN ROSENTHAL: Thank you, Dr. Kharesh. 3 We'll be moving along then to a new product, 4 which is AXERT, and Dr. Elgin will be rejoining us 5 for the presentation of this and the next product, 6 which are the Lamictal formulations. I'm sorry, Dr. 7 Notterman, but we'll need to ask you to remain 8 recused for both this discussion and for t.he 9 following one. Thank you. 10 (Pause.) 11 (Screen.) 12 AXERT (ALMOTRIPTAN) 13 DR. ELGIN: Is it okay if I just start? 14 Thank you. 15 This is a focused safety review on AXERT, 16 otherwise known as almotriptan malate. 17 (Screen.) 18 We're following a familiar outline. 19 (Screen.) 20 The original market approval was on May 7, 21

2001, and that was for adults with migraine with or

22

- without aura. Pediatric approval was obtained in
- 2 April 30, 2009, and that was for adolescents 12 to 17
- years of age.
- A written request was issued in October of
- 5 2001, amended in 2005, and exclusivity was granted
- 6 January 2009.
- 7 (Screen.)
- On to the pediatric studies in adolescents
- 9 12 to 17 years of age. There was a single-dose study
- in 12.5 milligrams, four-week, single-center, phase
- one PK and safety study, where there was 8 adults and
- 18 adolescents with migraines with and without aura.
- There was also a safety and efficacy phase 3
- double-blind randomized, placebo-controlled study.
- This was a dose-ranging study where the lowest dose
- was 6.25 milligrams and the highest was 25, as you
- can see, and then they had a placebo arm. So it was
- anywhere from about 170 to 186 patients.
- There was also a long-term multi-center
- 20 safety study, and that was just using the 12.5
- milligram dose, phase 3b open label, in adolescents
- with migraine with or without aura, multiple attacks

treated with a single dose.

2 (Screen.)

So the current indications now include adults with migraines, with or without aura, and also adolescents 12 to 17 years old with migraines, with or without aura, usually lasting four or more hours.

7 (Screen.)

8 So AXERT is almotriptan malate.

g (Screen.)

It comes in two different strengths, 6.25 and 12.5 milligram tablets. It's a triptan, a 5HT/1B/1D receptor agonist. The sponsor is Johnson and Johnson.

14 (Screen.)

have been labeling updates. There some 15 April 30, 2009, the warnings and precautions section 16 was labeled to update patients regarding potential 17 hypersensitivity to sulfonamides. Now, this was 18 based on a theoretical risk because AXERT is known to 19 contain a sulfonyl group and therefore it was felt to 20 be a potential cross-reactivity or cross-sensitivity 21 reaction in patients with a known hypersensitivity to 22

sulfonamides. So they put that in the label.

2 (Screen.)

On to relevant safety laboratory. Under the 3 warnings and precautions section, serious cardiac events, including myocardial infarctions, 5 threatening arrhythmias, have occurred. Patients 6 with a history of coronary artery disease either 7 don't take the drug or have proper evaluation before 8 they start. Patients with the signs and symptoms of 9 angina similarly had to be evaluated. 10 Cerebrovascular events, some of which have been 11 fatal, can occur with this drug. 12

13 (Screen.)

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Gastrointestinal ischemia; potentially lifethreatening serotonin syndrome can occur. This occurs when an individual is taking selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors. There could be an increase in blood pressure. And we already talked about the sulfonamides.

(Screen.)

So on to outpatient utilization data. We're

- dealing with -- we're defining the pediatric
- 2 population here, I should mention, as zero to 21
- years. Most of the time you're hearing presentations
- on zero to 16, but here we're going to zero to 21.
- 5 (Screen.)
- So during 2009, about a half a million, a
- 7 little bit more, Triptan prescriptions were dispensed
- in patients what fell into that pediatric age range,
- g zero to 21 years. Now, 55 percent of the triptan
- prescriptions, over 300,000, were dispensed for
- sumitriptan, Imitrex. Only 2 percent of triptan
- prescriptions, 12,600, were dispensed for AXERT, that
- we're talking about today.
- 14 (Screen.)
- So if you look at the AXERT outpatient
- utilization data for the year 2009, you've got about
- a quarter of a million prescriptions, about 80,000
- unique patients, and that includes both pediatric and
- 19 adult patients.
- 5 percent of AXERT prescriptions, 8.3
- 21 percent of AXERT patients, that's about 6,600
- patients, and 12,600 prescriptions.

1 (Screen.)

Top prescribing specialties were general practitioners, doctors of family medicine, osteopathy; and neurology. Top diagnosis, no surprise, migraine, for both adults and our defined pediatric population.

(Screen.)

2.1

This is just a pie chart to show you the spread -- does this thing work? It does. General practitioner, neurology, internal medicine. So you see where most of the prescribing specialties are coming from. It's just another illustration.

13 (Screen.)

Okay. Continuing with outpatient utilization data for AXERT, dispensed prescriptions peaked in 2003 with about around half a million prescriptions, down to 250,300 prescriptions in 2009. This includes both adults and pediatric patients.

So in the zero to 21 year age range there was a 46 percent decrease in dispensed prescriptions.

It went down from 23,400 in 2002 to 12,600 in 2009.

A similar thing happened in patients 22 years of age

- or older: 25 percent decrease in dispensed
- 2 prescription, down from 315,000 in 2002 to 237,000
- 3 plus in 2009.
- 4 (Screen.)
- 5 So the patient data parallels the
- 6 prescription data. Patients zero to 21 years of age,
- 55 percent decrease. You've got 14,800 patients in
- 8 2002. You go down to 6,600 patients in 2009.
- Adults, 141,400 in 2002; now you go down to
- 10 73,000 in 2009.
- 11 (Screen.)
- This is a graphic. You'll notice that they
- -- most of the triptan's being prescribed -- this is
- 14 sumitriptan here. This is a graph that includes
- other triptans which are used off label in the
- pediatric population commonly and that's why they are
- included in our analysis and presentation today.
- Sumitriptan has the lion's share of the
- market. That's the purple box at the top. Then if
- you look at the bottom, that's almatriptan. So here
- we go, this purple dot. It's way down here. So the
- use is quite low for AXERT.

1 (Screen.)

I don't want to spend too much time here in terms of diagnosis by age. Between the pediatric population and the adult population, it's quite similar for migraines and headaches otherwise specified.

7 (Screen.)

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Moving on to crude counts for adverse events, the total was 88. In the pediatric population there were five crude count adverse event reports. There were five serious. Five of them were serious. Two of them occurred in the United States. There was one death, which we'll talk about.

(Screen.)

Now we're going to talk about the death.

We're going over the time period of May 2001 when it

was approved up through June 25, 2010. So we have

this 18 year old female in 2003 who took one dose of

AXERT and died. Autopsy was unrevealing. A

cardiologist and a pathologist speculated about the

theoretical possibility of an arrhythmia.

The physician did not ascribe causality to

- 1 AXERT. She had had a history of chest pain on other
- 2 triptans. She didn't tolerate Imitrex or
- 3 sumitriptan. She was on topamax, which is another
- migraine medicine, for one year prior to two courses,
- 5 previous courses of AXERT, which she did tolerate
- 6 well. So we basically don't know what happened
- 7 here.
- 8 (Screen.)
- On to serious labeled adverse events. There
- is a case of serotonin syndrome. This was a 17 year
- old female in 2004 who experienced acute serotonin
- syndrome while taking an MAO inhibitor, phenelzine.
- 13 She experienced hyperpyrexia, hypertension,
- tachycardia, tremor. She was hospitalized. We do
- not know the final outcome.
- 16 (Screen.)
- There was a 20 year old female, 2004. She
- had an anaphylactic reaction. This came after the
- second dose of AXERT. She had started fluoxetine the
- day before this occurred. We do not know the dose of
- the fluoxetine. We do know she was hospitalized and
- $_{22}$  recovered after the drug -- after AXERT was

discontinued.

2 (Screen.)

Now we have a suicide attempt, again under 3 the category of serious labeled adverse events. This year old female was being treated 5 naratriptan. It didn't work, so they started a drug 6 called oxetorone. This is not approved in the United 7 States. It's a tetracyclic anti-serotoninergic drug, 8 and this can cause neurologic problems, including 9 coma, seizures, as well as cardiac conduction 10 abnormalities, and that's been reported with 11 overdoses on this drug. 12

So the normal dose for this drug is 60 milligrams roughly and she took 1800 milligrams of this stuff, along with 75 milligrams of AXERT. She was hospitalized with a GCS, or Glascow Coma Scale, of 6, extrapyramidal parkinsonian syndrome. She had arrhythmias. They stabilized her and transferred her to a psych ward.

20 (Screen.)

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Then there was another patient who had 22 what's described as a multi-drug reaction. I have to

- $_{\mbox{\scriptsize 1}}$  start out by saying that the documentation in the
- 2 report was conflicting and it is not entirely clear
- 3 whether or not this individual, this 17 year old
- $_{4}$  individual, actually took any AXERT at all, to be
- 5 honest about it.
- Other medications this patient was taking
- 7 included topiramate or Topamax, ibuprofen,
- ketoprofen, mirtazapine, and DHE. Many of the
- g reported adverse events in this patient are
- associated with the other medications, so it's
- difficult to draw a conclusion. We don't even know
- if this person got the drug.
- 13 (Screen.)
- Going on to unlabeled adverse events in
- adults over the age of 21 in AXERT. If we look at
- 16 crude counts from the time of its approval through
- June 25 of 2010, you've got two counts of amnesia,
- two falls, two retinal detachments, two suicide
- attempts, two episodes of trismus. Again, these are
- including duplicate reports.
- 21 (Screen.)
- We're going to sort of shift gears for a

- little bit and talk about the other triptans to give
- you a feel for how they compare with AXERT. Again,
- 3 we're defining the pediatric population as zero to 21
- 4 years of age.
- 5 (Screen.)
- There were two deaths. One was a 16 year
- old male who took in 350 milligrams of sumatriptan,
- and the maximum dose is 100, on the 27th or 28th of
- 9 December 2001. They think he may have taken an
- additional 100 milligrams the next day, plus one dose
- of zolmatriptan -- they don't know what the dose was
- 12 -- and some unknown amount of pseudofed.
- He progressed from lethargy, December 29th,
- to fixed and dilated pupils when he was found on
- December 30th. Apparently he had vomited. He became
- apneic and he went into asystole. He was pronounced
- brain dead, life support was withdrawn. Death was
- 18 determined to be from respiratory complications and
- idiosyncratic reaction versus suicide attempt.
- When I say we're talking about all the other
- triptans, I'm referring to Amotriptan, Sumatriptan --
- 22 Almotriptan; sorry, that's a typo -- Sumatriptan,

- Zolmitriptan, Rizatriptan, and Eletriptan, because
- these are used off label in the pediatric population.
- 3 (Screen.)
- Okay, we had a second death, and that was a 21 year old female in 1996. She got Sumatriptan subcutaneously. We do not have a narrative on this patient. We know that she was an asthmatic, taking salmeterol and albuterol. Preferred terms associated with this case include asthma, cardiac arrest, cerebral ischemia, and coma. We don't have any more
- 11 information than that.
- 12 (Screen.)

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- Serious unlabeled cardiovascular events in the triptans. We're going from the drug approval date for each one of these triptans, because they have different approval dates, through the end of
- So for Almotriptan, or AXERT, we had that

  one case of Bundle Bench Block, which was the

  intentional overdose I described to you previously.

June, close to the end of June 2010.

Then there was Sumatriptan. They had pulmonary valve stenosis, tricuspid valve

- incompetence, VSD. With Zolmitriptan, nothing;
- Rizatriptan, nothing; Eletriptan, that was the
- 3 Dressler's Syndrome, which is a multi-organ
- 4 hypersensitivity. We talked about that.
- These were chosen -- I already explained.
- These drugs were chosen because they're most often
- y used in the pediatric population, although they're
- not approved for use in the pediatric population.
- g (Screen.)
- Now, if you look at serotonin syndrome with
- these triptans, you just have almost one case each of
- serotonin. Rizatriptan has two. The age range in
- the patients is 17 to 20 years. One age was not
- 14 known. Interestingly enough, four of the five had
- 15 concurrent use of an SSRI. Duplicates were
- 16 eliminated from this count.
- 17 (Screen.)
- Okay. This concludes the pediatric focused
- safety review. The safety data has been incorporated
- 20 into the warnings and precautions section of the
- label -- that's 5.7 -- regarding the potential
- 22 hypersensitivity to sulfonamides, remember, because

- it's got the sulfano group.
- The FDA recommends continued routine
- monitoring. Does the committee concur?
- 4 CHAIRMAN ROSENTHAL: Thank you, ladies and
- 5 gentlemen.
- Yes, Dr. Holmes.
- 7 DR. HOLMES: So how many serious rashes have
- you seen with this drug? Has it been any higher than
- g the other triptans?
- DR. KASIM: My name is Suhail Kasim. I'm a
- 11 clinical reviewer in neurology.
- 12 Was the question how many serious rashes?
- DR. HOLMES: Right. I mean, you have it on
- the label and I guess that's what you're supposed to
- scare people about, and I just wonder if you've seen
- 16 it.
- DR. KASIM: I don't think so. We haven't
- 18 seen it.
- DR. FINE: My name is Andrew Fine. I'm a
- 20 safety evaluator in the Division of
- 21 Pharmacovigilance. In the process of this review
- there were not any cases of serious rash. From my

- understanding, this as presented was a theoretical
- label -- the language with the sulfonamides was it
- has a sulfano moiety; there's a theoretical risk of
- the rash and that was the reason for the label.
- 5 CHAIRMAN ROSENTHAL: Yes, Dr. Shwayder.
- DR. SHWAYDER: I want to know whether when
- you put things in the labels, do you put this as
- 8 theoretical? It would be really helpful to me,
- having been expert witness on some of these things in
- lawsuits, where the prosecuting attorney is waving
- the PDR in front of me and saying: See, see, the FDA
- has said it's a rash. I go: No, no, it doesn't
- happen; it's just theoretical. That would be very
- helpful if you'd throw it in there: This has never
- been seen, however it's theoretically possible.
- Think about it. Make our life a lot easier.
- 17 CHAIRMAN ROSENTHAL: Okay, all right. We
- 18 can add that to the to-do list.
- 19 Other comments regarding AXERT?
- 20 (No response.)
- 21 CHAIRMAN ROSENTHAL: Return to routine
- 22 monitoring, all in favor?

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(A show of hands.)
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                CHAIRMAN ROSENTHAL: Any opposed?
2.
                (No response.)
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                CHAIRMAN ROSENTHAL: I don't see
                                                         any
 4
       abstentions.
5
                (No response.)
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                CHAIRMAN ROSENTHAL: So, Dr. Wolfe?
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                DR. WOLFE: I yield to Dr. Towbin this time.
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                CHAIRMAN ROSENTHAL: Dr. Towbin.
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                DR. TOWBIN: Thank you very much.
                                                         Dr.
10
       Towbin agrees.
11
                DR. SHWAYDER: Tor Shwayder, agree.
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                DR. D'ANGIO: Carl D'Angio, concur.
13
                DR. RAKOWSKY: Alex Rakowsky, concur.
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                DR. SANTANA: Victor Santana. I agree.
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                MS. CELENTO: Amy Celento, concur.
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                DR. KRISCHER: Jeff Krischer, concur.
17
                DR. HOLMES: Greg Holmes, agree.
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                DR. WAGENER: Jeff Wagener, agree.
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                DR. LA RUSSA: Phil La Russa, agree.
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                DR. WOLFE: Sid Wolfe, agree.
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                CHAIRMAN ROSENTHAL: All right. Moving
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- 1 right along then, our next product will be Lamictal
- and Lamictal XR.
- 3 (Screen.)
- DR. ELGIN: I'm sorry, I forgot the
- 5 acknowledgments. These people are to be acknowledged
- and thanked for their contributions to this
- 7 presentation. I'm sorry, I forgot about that.
- 8 CHAIRMAN ROSENTHAL: Thank you.
- 9 LAMICTAL AND LAMICTAL XR (LAMOTRIGINE)
- DR. ELGIN: Now let's see what happens.
- 11 I've just got to go down here. Hold on.
- This is Lamictal and we're going to be
- 13 talking about Lamictal itself and also the extended
- 14 release product.
- 15 (Screen.)
- This is the focused safety review on
- 17 Lamictal XR, which is the extended release
- 18 formulation of Lamictal.
- 19 (Screen.)
- There's the outline.
- (Screen.)
- The original market approval for Lamictal

- itself was in December 27, 1994. Then they developed
- different formulations which were approved. So the
- 3 chewable, the dispersable tablets, were approved in
- August of '98. There was the orally disintegrating
- tablets, approved in May of 2009.
- In August of 1998, Lamictal labeling got a
- box warning regarding serious life-threatening and
- g fatal rashes in both the adult and pediatric
- 9 population. Pediatric exclusivity was granted in
- 10 February of 2007. Efficacy and safety studies were
- done in 1 to 24 month olds and in patients greater
- than or equal to 2 years of age.
- So the labeled formulations include the
- regular tablets, the chewable tablets, and the orally
- disintegrating tablets. The regular tablets have
- 16 gone generic.
- 17 (Screen.)
- The current indications include: adjunctive
- therapy of epilepsy in patients two years of age and
- older; generalized tonic-clonic seizures; partial
- seizures, with or without secondary generalization;
- 22 patients who have Lennox-Gastaut syndrome; patients

greater than or equal to 16 years of age as
monotherapy in selected individuals converting over
from other therapeutic agents; and also maintenance
treatment of bipolar I disorder in patients who are

at least 18 years of age.

6 (Screen.)

Now, in November of 2008 there was 7 Pediatric Advisory Committee and they supported the 8 from a July advisory committee recommendations 9 regarding the need to label for suicidality. So a 10 labeling change occurred in April of 2009 and that 11 added to the warnings and precautions section, 5.5, 12 of the label suicidal behavior and ideation. 13

14 (Screen.)

So we have Lamictal XR, which is the extended release formula. It's enteric-coated tablets. We know it's an anti-epileptic drug.

Smithkline Beecham is the sponsor.

19 (Screen.)

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This XR formulation was approved in May of 2009, and the original indication was for adjunctive therapy for partial seizures with or without

secondary generalization in patients who were at least 13 years of age.

3 (Screen.)

Then there were some labeling updates. In

January of 2010 this involved adding a new indication

so that it was now adjunctive therapy for primary

generalized tonic-clonic seizures in patients who are

at least 13 years of age, and then dosing titration

was updated in the label.

Then in April of 2010 they added a new dosing strength. They added a 300 milligram tablet to the other. You can see the other milligram tablet strengths on the slide.

14 (Screen.)

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Regarding pediatric studies for Lamictal XR, extended release, there was a 19-week, double-blind, multi-center, randomized, placebo-controlled study in 143 patients 13 to 16 who had had at least three primary generalized seizures at baseline.

There was a 19-week, double-blind, multicenter, randomized study in 236 patients greater than or equal to 13 years of age, but note that over 90 percent of them were 16 to 65 years of age, for partial onset seizures with or without secondary generalization, and they had a baseline of at least eight partial seizures during an eight-week baseline period.

In both of these studies, the patients received a fixed target dose in the range of 200 to 500 milligrams a day and they were allowed to take up to two other anti-epileptic medicines.

(Screen.)

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I wanted to mention a little bit about the relationship between the immediate release formulation of Lamictal and the XR formulation. The IR formulation of Lamictal for the treatment of partial seizures in the 12 to 18-year age range had over 90 percent congruence of bioavailability with the XR formulation. That was already approved for pediatric patients in the 13 to 16-year age range.

So a requirement to study Lamictal XR in the 1 month to 13 year age range was waived because of the IR-XR formulations exhibiting such a similar prescription behavior and dosing information was

- adequately labeled. 1
- (Screen.) 2.
- Moving on to relevant safety labeling with 3 Lamictal XR. You know about the life-threatening box 4 the They also warning of rash. 5 hypersensitivity which may not involve a rash, but 6 things like fever and lymphadenopathy. Multi-organ 7
- (Screen.)

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Blood dyscrasias, neutropenia, 10 You know about the thrombocytopenia. suicidal 11 ideation. Also, medication errors involving name 12 confusion. 13

failure has occurred on this medication.

- (Screen.) 14
- On to outpatient utilization data. 15 going from May 2009 to April 2010 and now we're 16 looking at all formulations. Approximately 9 million 17 dispensed prescriptions and 1.5 million unique 18 includes all the formulations. patients. That 19 That's the regular Lamictal, the generic, the orally 20 disintegrating, the chewable dispersable, and the XR. 21
- So 5 percent of these qo to 22

- prescriptions, go to the 13 to 16 year age range; 3
- percent to the 8 to 12-year age range; and 1 percent
- from zero to 7 years.
- 4 (Screen.)
- Now, if you just look at the XR formulation,
- in that same time frame you're talking about 75,000
- 7 prescriptions, 20,000 unique patients, which is
- g really less than 1 percent of the total lamotrigine
- 9 prescription market.
- 10 So if you look at the pediatric patients --
- and here we're defining zero to 16 years of age --
- you have about 11,500 dispensed prescriptions and
- 2,600 patients -- not a whole lot.
- 14 (Screen.)
- This is a graphic and it reminds me of some
- other graphs I've shown today. But you can really
- see the lion's share here is going to the -- I wish
- this would work -- lamotrigine in its generic form,
- lion's share of the market.
- Now, you see that yellow box there. The
- yellow box is the XR formulation that I'm supposed to
- be talking about today. If you look -- you have to

- look really, really way down at the bottom of that
- graph to see a yellow box. They're barely visible.
- That's how low the utilization is.
- Then of course, down below along with it is
- the chewable and the orally disintegrating.
- 6 (Screen.)
- 7 Prescriptions dispensed by age. I don't
- know that we need to dwell too much on this. The
- only thing I would point out is you see under the age
- 10 17 and older carrying the lion's share of
- prescriptions, over 8 million. Then second to that
- is patients age 13 to 16 with just under half a
- 13 million.
- 14 (Screen.)
- Regarding unique patients, we said there
- were 1.5 million of them. Again, the lion's share
- goes down to above the age of 17. There's 1.4
- million there. Next in line, but way, way down in
- terms of numbers, is ages 13 to 16 with about close
- 20 to 80,000.
- 21 (Screen.)
- 22 If you look just at Lamictal XR, extended

- 1 release, prescriptions and you look at that age
- breakdown in the pediatric population, you see that
- most of them are going, as I said, to the 13 to 16-
- year age range. There's your breakdown. Again, if
- you look at age 17 plus it's a lot bigger number.
- But the overall total number is only around 20,000,
- and that's not very big.
- 8 (Screen.)
- 9 Who prescribes the medications? For the
- 10 regular tablets -- that's the Lamictal and the
- generic version -- psych, 50 percent; neuro, 17
- percent. Chewable dispersable, neurology 43, psych
- 13 19. XR is primarily neurology. It's 68 percent.
- 14 Lamictal oral dispersable, psychiatry 58 percent and
- neuro much lower at 16 percent. (Screen.)
- 16 Diagnoses associated with lamotrigine
- products in general: epilepsy and bipolar disease.
- 18 (Screen.)
- This slide I don't want to dwell too much
- on, either, just to mention that -- you see that it's
- used both for epilepsy and there are some off-label
- psych uses, especially in the younger, zero to 7 age

- population. You see conduct disorder, psychoses. If
- you look at the above 17, you see mainly bipolar
- actually tops epilepsy.
- 4 (Screen.)
- Do we need to dwell on this? I don't think
- so. Let's move on. This is just a breakdown by the
- different formulations.
- For the XR formulation, I will say, if you
- g look at it, that breakdown is pretty much mostly
- epilepsy, not -- oh, there is bipolar in there, I
- should say. I'm sorry. Otherwise, epilepsy.
- 12 (Screen.)
- Moving on to crude counts for adverse events
- in Lamictal XR. Now, we had a total of 36. If we
- look at the pediatric population from zero to 16
- years of age, we've got five adverse events. Three
- of them are serious and they all happened in the
- U.S.; no deaths.
- 19 (Screen.)
- Now, these five reported adverse events
- represent 5 percent of the total of the 98 reported.
- 22 All of these patients were being treated for

- seizures and the age range was 7 to 16 years. The
- dosing range was 25 to 500 milligrams. Again, we're
- talking about the extended release formulation.
- 4 (Screen.)
- There were no reported cases in the extended
- 6 release formulation of hepatotoxicity, aseptic
- 7 meningitis, or life-threatening rashes, such as
- 8 Stevens-Johnson Syndrome or Toxic Epidermal
- 9 Necrolysis.
- 10 (Screen.)
- Going on to serious labeled adverse events
- for the XR formulation, from May 2009 to June 30,
- 2010, there was a ten year old on Depakote. He took
- 25 milligrams Lamictal XR every day. He was supposed
- to take it every other day. He got a rash and fever.
- 16 Depakote and Lamictal XR were discontinued. We
- don't know what happened after that; no further
- 18 history.
- 19 (Screen.)
- There was a 16 year old female on Zonegran,
- otherwise known as zonisamide, for seizures. She
- 22 began to take a 500 milligram dose of Lamictal,

lamotrigine, and the Zonegran was supposed to be tapered off, and she had a breakthrough seizure.

3 (Screen.)

There was a 14 year old on Keppra, otherwise 4 known as leveiracetam. Now, she was started -- it's 5 not clear from the report -- either on 50 or 100 6 milligrams of Lamictal XR. She experienced 7 activity, breakthrough seizure not otherwise 8 specified. She experienced fatigue, according to her 9 mother's report, going from the 50 to 100 milligrams, 10 but it really isn't clear when you read the report 11 what her real starting dose was. So difficult to 12 know how to interpret that. 13

14 (Screen.)

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Going on to non-serious labeled adverse events, there was a seven year old female with no reported history of any concomitant medication. She started Lamictal XR at 50 milligrams twice a day, had worsening of her nearsightedness and blurry vision. We don't know the outcome of that.

21 (Screen.)

There was a 15 year old female who was

- taking folic acid and clonazepam. She started
- 2 Lamictal XR 300 milligrams a day. She took 100 in
- 3 the morning, 200 at night, and she experienced
- bruxism. You all know what that is, right, where
- you're grinding your teeth.
- As far as we know, they discontinued her on
- 7 the Lamictal XR and there was no resolution of the
- bruxism as of the time of the reporting.
- g (Screen.)
- Moving on to just a comparative view of
- 11 crude counts for Lamictal XR, the chewable
- 12 dispersable formulation, and the orally
- 13 disintegrating tablets associated with serious
- outcomes. If you look at Lamictal XR, you'll see
- that there's only three, and we know that its use is
- quite low compared to the other products. It's
- higher in the chewable dispersable, 63 total; and
- orally disintegrated, 20 total.
- 19 (Screen.)
- 20 If you look at the crude counts of serious
- unlabeled adverse events related to the chewable
- dispersable form of Lamictal in children zero to 16

- 1 years of age, you have four counts of toxic shock
- 2 syndrome, three of autism, three of hypernatremia,
- 3 three of lactose intolerance, and two neunatal
- 4 cyanosis.
- Now, these are crude counts, so you have
- 6 duplicates in there.
- 7 (Screen.)
- So what we end up with non-duplicated cases
- of serious unlabeled adverse events, again Lamictal
- chewable dispersable, not the XR, we've got three
- 11 patients. One had toxic shock and hypernatremia;
- another one, autism and lactose intolerance; and the
- third patient, neonatal cyanosis.
- 14 (Screen.)
- The toxic shock syndrome patient, who also
- had hypernatremia, was an 11 year old girl who was on
- sodium valproate, who developed hair loss, which is a
- 18 known side effect of that drug. She started
- lamotrigine chewable dispersable and started to --
- the idea was to wean her of the Depakote.
- She developed a rash on day 13,
- rhabdomyolysis, hypernatremia, what they described as

- toxic shock syndrome, and multi-organ failure. Both
- 2 seizure medications were stopped. She had a full
- 3 recovery post-hospitalization and the sodium
- 4 valproate was restarted.
- 5 Dermatologists later thought that it was a
- 6 drug reaction with eosinophilia and systemic
- y symptoms, known as DRESS, or otherwise known as
- 8 multi-organ hypersensitivity. So that's what they
- ended up in the end thinking had happened to her.
- 10 (Screen.)
- 11 Then we have a case of a 14 year old with
- autism and a history of fungal infections and lactose
- intolerance, on an anti-candida diet and taking a lot
- of nutritional supplements. She was -- she was
- taking Lamictal CD 125 milligrams a day and dylatin,
- or phenytoin, 340 milligrams a day, for seizures that
- 17 had begun in 2005.
- 18 We don't know when her autism was diagnosed.
- The physician comments that the autism was due gut
- 20 dysbacteriosis and not lamotrigine chewable
- dispersable. I cannot make any further comments on
- how he arrived at that conclusion.

1 (Screen.)

Serious unlabeled events, continued. Now we have this case of neonatal cyanosis. Now, we have a neonate's mother who was pregnant with her baby, receiving 875 milligrams a day during the pregnancy, and the plan was to wean her off by 20 milligrams a week after she gave birth.

The normal dosing for Lamictal is 200 to 500 milligrams. But it depends on the patient and the use of other medications. The clearance of Lamictal during pregnancy may increase from 65 to as high as 300 percent, and that's why she was on such a high dose.

14 (Screen.)

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She gave birth and at 16 days she was 15 breastfeeding her baby boy and he had a brief episode 16 of apnea, and then three hours later he developed 17 This woman physician. cyanosis. was а 18 administered six minutes of chest compressions, 19 resulting in normal color with spontaneous 20 respirations. 21

(Screen.)

- Now, his serum level was 4.87 micrograms per
- 2 ml. The proposed pediatric therapeutic range is 1 to
- 5 micrograms per ml. The actual neonatal therapeutic
- range, we don't know what that is.
- Breastfeeding was continued until day of
- 6 life 17. The patient had an uneventful recovery.
- 7 Currently in the labeling in in section 8.3
- g it says: "Preliminary data indicate that lamotrigine
- 9 passes into human milk. Because the effects on the
- infant by this route are not known, breastfeeding
- 11 while taking Lamictal XR is not recommended." So
- they say don't breastfeed.
- 13 (Screen.)
- Now, lamotrigine is metabolized
- predominantly by hepatic glucuronidation and it's
- also renally excreted. Maternal lamotrigine serum
- levels and half-life can vary enormously, from 6 to
- 18 103 hours, vary widely between patients, because of a
- host of genetic differences, glucuronidation, mainly
- due to different isoenzymes present and the use of
- 21 concomitant medications which could definitely
- influence levels. They can either induce or inhibit

- glucuronidation.
- 2 (Screen.)
- 3 Infants have relatively high plasma levels,
- 30 to 35 percent of maternal serum levels. Now,
- glucuronidation needed to metabolize lamotrigine is
- not mature in infants until they're two to six months
- of age.
- 8 There's another problem in that the neonates
- have immature renal excretion. Normal eGFR takes six
- months and even up to as long as two years to fully
- develop in some patients.
- 12 (Screen.)
- So the safety of lamotrigine has not been
- systematically assessed in neonates, infants, or any
- children less than two. The approved pediatric
- lamotrigine starting dose -- that's the general
- lamotrigine, Lamictal -- in patients 2 to 12 years of
- $_{18}$  age is 0.15 to 1.2 mgs per kg per day. The
- maintenance is usually 1 to 15 mgs per kg per day,
- depending on what other meds they're taking, if they
- are taking other meds.
- The lamotrigine what's called the relative

infant dose was calculated at less than 10 percent in 1 a few of the small studies from the literature that 2. was reviewed by the maternal health staff. They were 3 consulted on this. However, the theoretical infant doses used in these relative infant dose calculations 5 generally fell within or above the 6 therapeutic doses for kids 2 to 12 years of age, 7 children 2 to 12. 8

(Screen.)

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So despite the high infant lamotrigine doses received through human milk, there has been only one serious adverse reaction that we know about reported in a breastfed infant. Reports are limited. No data exists on the long-term neuropsychological and developmental outcomes in infants who are exposed to lamotrigine through human milk or in utero. We don't know much about it.

(Screen.)

This completes the pediatric focused patient review. Safety data from PREA studies have been incorporated into the label. The FDA will continue to monitor adverse events associated with

- breastfeeding and routine monitoring.
- 2 Please comment, if you will, on the
- following options: continue monitoring for
- additional breastfeeding-associated cases in infants
- 5 before making any labeling change; revise the
- 6 labeling to include lactation data from the
- 1 literature to better inform lactation risk-benefit
- decisionmaking; or, if you will, any other
- g recommendations you have.
- 10 CHAIRMAN ROSENTHAL: Do you have an
- acknowledgments slide?
- DR. ELGIN: Oh.
- 13 (Screen.)
- DR. ELGIN: What is it with me? I'm trying
- to claim all the glory.
- Yes, I do, and I thank all these people for
- their contribution to this presentation. Thank you.
- CHAIRMAN ROSENTHAL: I thought you were just
- 19 testing me.
- DR. ELGIN: No.
- 21 CHAIRMAN ROSENTHAL: Can you go back one?
- (Screen.)

- 1 CHAIRMAN ROSENTHAL: Yes, Dr. Shwayder.
- DR. SHWAYDER: Does the current labeling
- mention anything about breast milk?
- DR. ELGIN: It says not to breastfeed in
- section 8.3 if you're taking XR, in the XR label,
- 6 which is separate from the regular label.
- DR. FARRAR: Was this regular lamotrigine or
- 8 was this XR, this neonatal case?
- 9 DR. ELGIN: This was --
- DR. FARRAR: I thought it was the regular
- 11 lamotrigine.
- DR. ELGIN: I think it was the regular one.
- DR. SIMMS: The dosage form isn't specified
- in the report.
- 15 CHAIRMAN ROSENTHAL: Yes, Dr. Goldstein.
- DR. GOLDSTEIN: Were there pre-clinical
- 17 studies that looked at lamotrigine in breast milk in
- 18 mammals?
- DR. ELGIN: I have to defer to neurology. I
- don't know the answer to that question.
- DR. HERSHKOWITZ: I would suspect that there
- were, but you have to remember that in our maternal

- 1 health we have found a lot of literature on its
- excretion in breast milk. So I think those are in a
- 3 sense moot. The label itself says it's possibly
- distributed in breast milk, but we think that that
- should be more definitive and that it is excreted in
- 6 breast milk.
- 7 DR. MURPHY: Will you introduce yourselves,
- too, please, the division?
- 9 DR. HERSHKOWITZ: I'm sorry?
- DR. MURPHY: Would you introduce yourself,
- 11 please.
- 12 CHAIRMAN ROSENTHAL: May I ask the people
- down -- our colleagues from neurology to please
- introduce yourselves into the microphone, so that
- we've got a record.
- DR. HERSHKOWITZ: I apologize.
- 17 CHAIRMAN ROSENTHAL: thank you.
- DR. HERSHKOWITZ: I'm also a little hard of
- 19 hearing.
- I'm Norman Hershkowitz. I am a DNP,
- 21 Division of Neurology Products, team leader who is
- involved in this drug, and all anti-convulsants, for

- 1 that matter.
- 2 CHAIRMAN ROSENTHAL: And your colleagues?
- DR. DINSMORE: Steve Dinsmore, medical
- reviewer for DMP for the anti-convulsants also.
- DR. SIMMS: I'm Kelly Simms. I'm a safety
- evaluator from the Division of Pharmacovigilance.
- 7 DR. BEST: I'm Jeanine Best. I'm a clinical
- g reviewer on the Pediatric and Maternal Health Staff,
- both Maternal Health and Pediatric teams, and I did
- 10 the lactation review.
- 11 CHAIRMAN ROSENTHAL: Thank you.
- Dr. Goldstein, will you repeat your
- 13 question.
- DR. GOLDSTEIN: My question was was there
- pre-clinical data that supports that lamotrigine is
- 16 excreted in breast milk, and the follow-up to that
- is, assuming there is and there's now clinical data,
- I couldn't agree more that the label should change.
- DR. HERSHKOWITZ: Again, I suspect there is.
- That data is usually included, but it's not in the
- label. I can't definitively say. But let me refer
- to Maternal Health.

- DR. BEST: Generally, all you can gain from
- the animal data is whether it's excreted into milk or
- not. The amount that excretes into an animal,
- sure because once they have the human data, once they
- put the human data in the labeling, the animal
- 7 excretion data to human milk is irrelevant after
- g that.
- DR. GOLDSTEIN: Well, it doesn't become
- irrelevant if -- what's the wording that is currently
- 11 used?
- DR. HERSHKOWITZ: I believe it says
- 13 "preliminary data."
- DR. GOLDSTEIN: As soon as you have pre-
- clinical and clinical data, it goes out of the realm
- of preliminary in my opinion.
- 17 CHAIRMAN ROSENTHAL: Dr. Holmes.
- DR. HOLMES: It just seems to me a great
- disservice to have that on the label, that the mother
- shouldn't breastfeed if they've been taking
- lamotrigine, based on one case. I mean, all the
- anti-epilepsy drugs are excreted in the breast milk.

- 1 It depends on the protein binding of the drug.
- And to base this -- the baby's been bathed
- in lamotrigine for nine months, and then to say,
- $_{oldsymbol{arphi}}$  well, because they don't have glucuronidation the
- level's going to go up a little bit -- I mean, I can
- tell you that recommendation is not being followed by
- many, many people.
- DR. HERSHKOWITZ: If I can respond to it,
- the label says it's not recommended. It doesn't say
- don't do it. And indeed, the Med Guide I believe has
- 11 a statement stating that you should talk to your
- physician about the risk and benefit of it.
- 13 Certainly we don't want to prevent it, but
- we will change the labeling to something -- I can't
- tell you exactly what, but we're going to discuss
- this. We'll probably get rid of the "preliminary
- data." We'll probably mention this case, and there
- 18 were some other cases of somnolence, and that
- children should be monitored during this period.
- But again, by stating recommended it's not a
- contraindication. Again, the Med Guide does leave
- open the possibility of a risk-benefit decision.

- believe -- don't you have in your review --
- DR. MURPHY: Just one other thing. Again,
- 3 because of this, OSE has, Office of Surveillance, has
- done an additional, because that was just from the
- one year. It came in last night, so this is a very
- 6 preliminary assessment of what's in that.
- 7 DR. SIMMS: Yes. The Division of
- 8 Pharmacovigilance just completed a review of the
- g lamotrigine exposure via breast milk using our
- adverse event data that's in our AERS database. We
- also found an additional 18 cases which we haven't
- discussed internally in the agency. So there's more
- than just that one literature case that seems to be
- 14 serious.
- DR. McMAHON: I'd like to just add a little
- bit to that, which is that the one case that was
- presented here was really quite well documented,
- especially for AERS. It really had some numbers and
- things associated with it. A lot of the other cases
- are not quite as well documented. I just wanted to
- 21 put that on the table.
- CHAIRMAN ROSENTHAL: The agency is

- considering the analysis that was just completed late
- 2 last night and has not yet had time to completely
- g process this information; is that a correct
- 4 understanding?
- DR. McMAHON: That's right.
- 6 CHAIRMAN ROSENTHAL: Other questions -- oh,
- 7 I've got -- I'm sorry. I've got Doctors Towbin,
- Rakowsky, and Farrar on my list. Dr. Towbin.
- DR. TOWBIN: Well, I believe my question was
- answered by the previous comments to a great degree.
- I just want to be sure that I understood that one of
- t options that's being considered is a strengthening
- of the language to indicate that there could indeed
- be quite a risk of breastfeeding, something stronger
- than it's just not recommended.
- DR. HERSHKOWITZ: You know, again, we
- haven't discussed this internally fully. But the
- first thing we want to get rid of is the "preliminary
- data," because we think that there's more than
- 20 preliminary data.
- The other thing, we will probably discuss
- issues of monitoring children. You know, it's hard

to say because this is going to be a discussion 1 amongst many people, and some people higher than my 2. level is presently. But I suspect our negotiations 3 will go something to the effect of get rid of the preliminary and describe -- there were some cases of 5 somnolence, some poor feeding. Describe -- and you 6 see, one of the issues here is that during pregnancy 7 you're bumping up the dosage because there's greater 8 clearance in the mother. 9

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Then the mother comes off, and if you're not cognizant of that -- you have to lower the dose again. So we want to increase the awareness of that phenomenology.

But we'll probably say -- but we'll still 14 say -- I don't think we'll change it from it's not 15 recommended, but we might -- we'll put benefit-risk. 16 Let me read to you what it states in the Med Guide, 17 which is slightly different. It says: "Before 18 taking Lamictal, tell your health care provider about 19 your medications, including if you 20 breastfeeding. Lamictal can pass into your breast 2.1 milk. You and your health care provider should 22

- decide if you should take Lamictal or breast feed."
- Well, I guess that is pretty significant.
- 3 "Breastfeeding while taking Lamictal is not
- 4 recommended." That's pretty actually typical
- language.
- But we'll have to discuss it amongst
- ourselves. This was a well documented case. There
- are a few other cases.
- DR. MURPHY: Our goal is to make the label
- as informative as possible, so people can make their
- own risk-benefit assessments. So what you're hearing
- is we had the one case, they scrambled to see if
- there were any more, there are some more, and we will
- 14 try to make the label more informative, without
- giving any definitive what that's going to look like.
- 16 Could you put the question back up again,
- 17 please?
- 18 (Screen.)
- So right now we're asking you if you have
- 20 any -- to discuss the options of just -- of these
- 21 options.
- DR. HERSHKOWITZ: But let me add again, "not

recommended" is not "contraindicated." 1

into breast milk.

- CHAIRMAN ROSENTHAL: Dr. Farrar and then Dr. 2
- Towbin. 3

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- I would like to reiterate what DR. FARRAR: Dr. Holmes said, and that is a lot of anti-convulsant 5 drugs, if you start contraindicating those then 6 there's just -- I would agree, I think what you have 7 to do is maybe take out the word "preliminary," but I 8 think this is still a decision that the doctor and 9 the family has to make, because there are not a lot 10 of options, because all these drugs -- when you get 11 right down to it, there's not a drug that does not go
- We can dance around it somehow or another 14 every now and then and say, well, not that much. 15 the reality is everything goes into breast milk 16 because every drug goes everywhere in every human 17 body if you give it enough time. 18
- So I think you just have to make the data as 19 rich as you can, which is what it sounds like you are 20 planning on doing, and then sort of leave it up to 21 people to kind of go from there. 22

- 1 CHAIRMAN ROSENTHAL: Dr. Towbin.
- DR. TOWBIN: Well, as a bit of a testimonial
- 3 to the high quality of the presentation, I think
- there are actually two things to be said about this.
- 5 One is that indeed the doses in pregnant women may
- have been elevated because of their increased
- 7 clearance.
- 8 Then the second hit is the infant cannot
- g clear this drug effectively. So I think the Med
- 10 Guide might need to spell that out, that it's a
- problem about things passing into breast milk, but
- also that very young children are not capable of
- 13 clearing the drug as efficiently and so there's a
- 14 greater risk for them.
- 15 CHAIRMAN ROSENTHAL: I think that's very
- 16 helpful.
- Other Dr. Holmes?
- DR. HOLMES: Just a couple quick questions.
- 19 Where did you come up with the 5 micrograms for
- 20 being the upper limits of toxicity, because that's
- 21 much lower than most clinicians would consider?
- realize there's not a lot of data on newborns.

- The other point, it may just be worthwhile to have people check levels in the babies if they're sleepy.
- Dr. Holmes, the last CHAIRMAN ROSENTHAL: said might that you be formulated as 5 recommendation to consider monitoring of the infant 6 if the medication can't be avoided in terms of the 7 the mother's epilepsy management of or other, 8 whatever her indication is, and that breastfeeding is 9 the only viable option for the child, or something 10 like that? 11
- DR. HOLMES: We're not going to -- I Yes. 12 wouldn't say it's the only viable option. 13 actually encourage breastfeeding in these mothers. 14 But I think putting everything in that was just said, 15 full disclosure, is the way to go. Part of full 16 disclosure may be to say, why not check some levels 17 if you're concerned about the baby. There's a lot of 18 people using it. 19
- 20 CHAIRMAN ROSENTHAL: So a carryover idea 21 from yesterday's meeting. The FDA is not interested 22 in regulating breastfeeding, so we'll have to word it

in some way that doesn't imply that they are.

DR. SIMMS: Going back to your previous question, the reference range was mentioned in the literature case, and the information comes from the Pediatric Dosage Handbook for the lamotrigine level.

DR. BEST: Another interesting fact about this case was that this mother had had a seizure during her pregnancy, so her doses were elevated much higher than normal. And she also had another seizure immediately postpartum, so she wasn't down-titrated as quickly in the first two to three weeks as most women are. She was actually having toxic effects or she was showing signs of drug toxicity herself.

A second interesting -- an article just published last week in Neurology, some preliminary analysis of a long-term neurodevelopmental study going on in children who have been exposed in utero to carbomazepine, lamotrigine, phenytoin, and valproate. What they're looking at, they gave the preliminary analysis of three year olds' cognitive data, and they're showing -- they compared both children exposed in utero who were then either

- breastfed or not breastfed, and they're showing --
- 2 the preliminary analysis right now is showing no
- difference in neurodevelopment and cognitive outcomes
- 4 between those two groups.
- 5 That was just published last week.
- 6 CHAIRMAN ROSENTHAL: That's helpful.
- 7 Let's get back to the question specifically.
- First let me ask the division whether the discussion
- 9 -- this doesn't seem like it's framed as a voting
- question. It seems like it's more framed in a way to
- 11 promote discussion.
- Have we achieved your objectives, or is
- there something specific that we need to -- shall I
- try and frame this in a way that we can take a vote?
- DR. MURPHY: Well, I guess this was trying
- to say you could say that, we think you should
- monitor only, and then you could vote on that. Or
- you should say, you need to revise the label. But it
- 19 was trying to lay out the different options. But I
- think the discussion has basically eliminated the
- "just continue monitoring."
- 22 CHAIRMAN ROSENTHAL: Yes. So let's vote on

- it, just to be very clear. How many people are in
- 2 favor of continuing current monitoring without any
- label changes, without any label changes?
- 4 (No response.)
- CHAIRMAN ROSENTHAL: How many people are
- 6 opposed to that?
- 7 (A show of hands.)
- 8 CHAIRMAN ROSENTHAL: And any abstaining?
- 9 (No response.)
- 10 CHAIRMAN ROSENTHAL: So it looks like
- there's uniform opposition to the notion of continued
- monitoring without any label changes. Dr. Towbin,
- will you start going around?
- DR. TOWBIN: Yes. Kenneth Towbin, agree
- with the label change.
- 16 CHAIRMAN ROSENTHAL: Let me just clarify.
- You are not in favor of continuing --
- DR. TOWBIN: To leave the label as is?
- 19 CHAIRMAN ROSENTHAL: Yes.
- DR. TOWBIN: Correct. If the motion -- if I
- didn't understand the motion, forgive me.
- 22 CHAIRMAN ROSENTHAL: I did it in reverse.

- DR. TOWBIN: I think that I'm voting to
- agree with a label change. Do I understand the
- 3 motion correctly now?
- A CHAIRMAN ROSENTHAL: Yes, you're voting
- 5 against leaving things the same.
- DR. TOWBIN: Correct.
- 7 DR. D'ANGIO: Carl D'Angio, opposed to
- leaving things the same. And I assume I'll get to
- yote for something in a bit.
- DR. RAKOWSKY: Rakowsky. Again, I agree --
- 11 I disagree with just continuing monitoring without
- any label change.
- DR. SANTANA: Victor Santana. I do not
- agree to leave things the way they are.
- MS. CELENTO: Amy Celento. I'm opposed to
- monitoring with no label change.
- DR. KRISCHER: Jeff Krischer, also opposed
- with no label change.
- DR. HOLMES: Greg Holmes, opposed to no
- label change.
- DR. WAGENER: Jeff Wagener, opposed.
- DR. LA RUSSA: Phil La Russa, opposed to

- monitoring with no label change.
- DR. WOLFE: I agree that we should change
- 3 the label.
- 4 CHAIRMAN ROSENTHAL: It wasn't meant to be
- 5 hard.
- So the next question is -- well, one
- question is should the label be revised to include
- lactation data from the literature. I guess if the
- g literature is something beyond what we've just seen,
- 10 I don't feel like we have much information to comment
- on that. But if the literature is just the case that
- we just reviewed -- yes, Dr. Wolfe.
- DR. WOLFE: I think I would just modify that
- question: Should the label -- revise the label to
- include lactation data from the literature and the
- ongoing and hopefully almost done extra cases they
- picked up. We want to be informed by that as well.
- CHAIRMAN ROSENTHAL: Thank you. You saved
- me a vote. So let's frame it that way. How many
- 20 people would be in favor of revising the label to
- include lactation data from the literature and from
- the ongoing studies?

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(A show of hands.)
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                CHAIRMAN ROSENTHAL: Any opposed?
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                (No response.)
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                CHAIRMAN ROSENTHAL: Any abstentions?
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                (No response.)
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                CHAIRMAN ROSENTHAL: Dr. Wolfe, since you
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       framed it --
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                DR. WOLFE: I agree.
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                DR. LA RUSSA: Phil La Russa. I agree.
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                DR. WAGENER: Jeff Wagener. I agree.
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                DR. HOLMES: Greq Holmes. I agree.
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                DR. KRISCHER: Jeff Krischer. I agree.
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                MS. CELENTO: Amy Celento, agree.
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                DR. SANTANA: Victor Santana. I agree.
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                DR. RAKOWSKY: Alex Rakowsky, agree.
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                DR. D'ANGIO: Carl D'Angio, agree.
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                DR. TOWBIN: Kenneth Towbin. agree.
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                CHAIRMAN ROSENTHAL: May I ask the division
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       what might be a reasonable time fame for you to
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       circle back to the PAC and share with us the output
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       from your ongoing investigations? I'm not trying to
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       put you on the spot. I'm just trying to -- I'm just
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- trying to figure out when we might anticipate this.
- DR. HERSHKOWITZ: I'm going to give a very -
- I'm going to be very liberal to us. I don't think
- $_{A}$  this is a -- all the reviews have been done. It's
- 5 just a matter of us getting together and making
- recommendations, composing it -- coming to some
- agreement as to what it should say, composing it, and
- asking the sponsor. The reviews have been done. Can
- 9 you give us a year until we actually have a response
- from -- I think we can do it in months, but then back
- and forth from the sponsor and all. So a year for
- the labeling change, I would say.
- 13 CHAIRMAN ROSENTHAL: So we have a spring
- 14 meeting and a summer meeting planned right now. You
- think the summer's more realistic, or you think the
- 16 fall meeting?
- DR. HERSHKOWITZ: No, I would do December.
- 18 CHAIRMAN ROSENTHAL: Okay.
- DR. HERSHKOWITZ: Again, these things can
- bounce back and forth from us to the sponsor.
- 21 CHAIRMAN ROSENTHAL: This isn't a contract.
- 22 We just want to get an idea. Thanks.

Yes, Dr. Wagener.

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DR. WAGENER: I just wanted to follow up on 2 something that Greg said earlier, and that is the 3 statement that says it recommended not to breastfeed, that's sort of an anti-pediatric approach right now; 5 and should instead we follow and say: This comes 6 across in the breast milk, there may be side effects 7 to the infant, levels could be followed in the infant 8 if that's the case, and get rid of the wording that 9 says we recommend against breast feeding. 10

Do we have data that would say that breastfeeding is harmful in the absence of these other potential safety margins? I would point out that one case, the level, the blood level, was in the range that supposedly is therapeutic. It was not excessive, and the child very likely had nothing related to the drug.

18 CHAIRMAN ROSENTHAL: Can we defer on that
19 until the current investigation is complete, because
20 I think that might inform this question. But your
21 point is a good one.

DR. MURPHY: We heard you. We'll consider

- that in the discussions. We've heard your thoughts.
- That's what you're here for, so thank you.
- 3 CHAIRMAN ROSENTHAL: Now, I promised that
- we'll adjourn on time at 5:45. We have one more
- 5 presentation, for Depakote, which will be presented
- by Dr. Lisa Jones. Dr. Jones is a senior reviewer on
- 7 the safety team within the FDA's Division of
- 8 Neurology Products. She received her MPH from
- Columbia University and is board-certified in public
- 10 health and preventive medicine.
- 11 I'll also just note for the record that Dr.
- Notterman has rejoined us and we're happy to have you
- 13 back.
- 14 (Screen.)
- DEPAKOTE ER (DIVALPROEX SODIUM)
- DR. JONES: This presentation will be
- summarizing the review of neurodevelopmental delays
- 18 following prenatal exposure to valproic acid and its
- reviewed within the Division of Neurology Products.
- 20 (Screen.)
- DR. MURPHY: I just want to point out this
- is a requested follow-up.

- 1 DR. JONES: Yes. Sorry.
- 2 CHAIRMAN ROSENTHAL: Thank you.
- DR. JONES: That's in the slide, but thank
- 4 you.
- 5 (Screen.)
- In this presentation the slides are divided into three groups. The first slides present some regulatory background on valproate. The subsequent slides describe the prior review within the Division of Neurology Products, a review that took place prior to the former presentation to the advisory committee.
- The third group of slides describes the review following the advisory committee.
- 14 (Screen.)
- At the time of the prior advisory committee, the committee shared the FDA's concerns regarding the potential safety signal, but agreed that the FDA's review should be ongoing and discussed potential methods to further the analysis.
- 20 (Screen.)
- Valproate is an older drug. it was first approved in the U.S. in 1978 for seizures in

- epilepsy. Subsequently, it's been approved for manic
- 2 episodes associated with bipolar disorder in '95,
- 3 with adjunctive and monotherapy treatment of complex
- partial seizures in patients over age ten in '96, and
- for migraine prevention in 1997.
- One might think that the majority of usage
- yould be in female patients, would be for epilepsy,
- but actually drug usage data examined by the division
- g shows that about half of female patients taking
- valproate were using it for indications other than
- 11 epilepsy. These included the approved indications of
- bipolar disorder and migraine prevention, as well as
- a variety of off-label uses, which were primarily
- 14 psychiatric.
- 15 (Screen.)
- Valproate is an established teratogen. It's
- widely known to produce a Fetal Valproate Syndrome
- with characteristic facial and other malformations,
- as well as neurologic manifestations.
- Valproate is classified as pregnancy
- 21 category D, which states that "Studies, adequate
- well-controlled or observational, in pregnant women

have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk."

And the teratogenicity is considered serious enough that it is described within the boxed warning, especially with regard to the risk of neural tube effects.

(Screen.)

This is a sample of the language from the boxed warning, and it states that: "The use of Depakote tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus." The issue is also discussed in more detail in the warnings section of the labeling.

(Screen.)

Prior to summarizing the division's review, this one slide presents some information on neurodevelopmental delays in general, which in humans is a fairly broad term, but generally refers to a deficit or delay in reaching expected cognitive andor social milestones or other measures that would be appropriate for age.

1 (Screen.)

2 It can be measured in a variety of ways.

3 There can be a medical assessment or diagnosis.

There are screening tools such as the Bayley Infant

5 Neurodevelopmental Screener, or IQ testing.

The developmental delays are believed to have a neurologic basis, but often etiology is

g unclear.

g (Screen.)

As part of the review, which began in the 10 in 2007, the division considered division the 11 relevant animal data. The valproate label notes that 12 "behavioral deficits" have occurred in rats with 13 prenatal exposure of 200 milligrams per kilogram per 14 day, which is equivalent to about half of the maximum 15 human daily dose. 16

17 (Screen.)

As mentioned, the review began in late 2007 or early 2008, and it was prompted by the publication of a growing number of public literature reports on the issue. At approximately the same time, the sponsor took note of the publications as well and

- submitted a report on the subject to the FDA.
- 2 (Screen.)
- In the FDA's review, the literature search 3 found that the largest of the studies on the subject was an interim report of the NEAD study, which was 5 just mentioned in the discussion preceding this 6 The "NEAD" acronym stands presentation. 7 "Neurodevelopmental Effects of Antiepileptic Drugs," 8 and the study is being performed by Dr. Meador and 9 colleagues. 10
- This is a prospective study. It's 11 prospective cohort study in which pregnant women with 12 epilepsy from the U.S. and U.K. enrolled from 1999 to 13 tracks cognitive outcomes Ιt among 14 children, and they're divided into four groups. 15 There are children who have prenatal exposure through 16 mothers treated with either carbamazepine, 17 lamotrigine, phenytoin, or valproate monotherapy. 18
- The study's primary outcome is IQ at age six. That has not -- that outcome has not been reached yet, and in 2007 the data that were available were from age two.

1 (Screen.)

The NEAD study collected a large amount of data on potential confounders, and included maternal age, IQ, seizure frequency, dose, birth weight, as well as smoking, alcohol, prenatal folate use.

At age two, the protocol specified that blinded examiners were to administer the Mental Development Index of the Bayley's Scales of Infant Development, and they would calculate the mean MDI adjusted for maternal IQ, maternal age, and AED dose.

(Screen.)

This slide presents the age two data, and you can see again for the four -- the children exposed in utero to the four monotherapies. As you can note on the slide, valproate has the lowest point estimate of the MDI scores. As you may also note, there is considerable overlap between the confidence intervals.

(Screen.)

At this point in the review in 2007, the division was considering various factors that influenced assessments of causality. The first was,

- as just mentioned, that although valproate had the lowest point estimate, there was considerable overlap
- 3 between the confidence intervals.
- In addition, as mentioned, it utilized the
- $_{\rm 5}$   $\,$  Bayley MDI as a testing instrument, and this is as a
- surrogate for IQ, a pre-IQ test for younger children.
- 7 Assessments in the literature which have looked at
- its correlation with subsequent IQ tests have had
- 9 mixed results or shown mixed results.
- In addition, there were only a small number
- of patients within the individual AED monotherapy
- subgroups, and particularly there were only 29 with
- valproate exposure who had an assessment at age two.
- 14 Finally, the division was aware that this
- was preliminary data, with a main outcome at age six.
- 16 (Screen.)
- At the time of the presentation, the prior
- presentation to the committee, the division decided
- not to pursue regulatory action at that time, and
- that decision was based on three issues. The first -
- or three reasons. The first were the issues that
- were just discussed in the previous slide.

The second was the knowledge that additional data from the NEAD study would be available in the near future, allowing for a more -- oh, thank you so much; thank you so much -- allowing for more informed regulatory decision.

And third was the fact that the valproate label already contained the boxed warning cautioning against use in pregnancy whenever possible.

(Screen.)

In April of 2009, two months before the first presentation to the committee, the second interim report of the NEAD study was published, and it presented results at age three.

14 (Screen.)

These results differed from the results at age two in that a different testing instrument was used. This time the Differential Ability Scale Score was used. As with the age two data, VPA, valproate, continues to have the lowest point estimates, although now the confidence intervals are beginning to diverge.

(Screen.)

Also at the time of the prior -- outstanding 1 issues at the time of the prior advisory committee 2. presentation included that: mothers treated with 3 valproate differed at baseline significantly from mothers who were receiving other AEDs, and they 5 differed primarily on breastfeeding, with 30 percent 6 of valproate mothers breastfeeding compared to 7 percent for the other AED monotherapies; and 8 addition particularly with regard to seizure type, 9 with most of the valproate-treated mothers having 10 generalized seizures. 11

12 (Screen.)

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Secondly, although the authors asserted a dose-response relationship for valproate and lower DAS scores, the division did not have access to the actual raw data at that time.

17 (Screen.)

Since the prior presentation, the division has pursued those outstanding issues.

20 (Screen.)

The NEAD investigators were kind enough to 22 share their data set with the FDA, and this was

evaluated by the FDA statisticians to assess whether 1 the appropriate statistical methods were used in 2. reaching and assessing the study conclusions,

3 especially with regard to the dose-response analysis.

(Screen.) 5

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statisticians' review and the conclusions reached by the study authors were generally in alignment, but the statisticians, the FDA statisticians, did raise a number of issues with regard to the analysis. The first of these issues, noted previously, was that there as were statistically significant baseline differences in on multiple factors groups and, treatment mentioned before, particularly with regard to seizure type.

The NEAD investigators acknowledged these differences, but noted that when the results were stratified by seizure type the children treated with valproate continued to have the lowest testing scores, and these baseline differences were likely associated with the treatment received.

Secondly, at age three there а 22

- 1 considerable amount of data that was missing and
- 2 needed to be imputed for 77 children, which was 25
- g percent of the total cohort. So this may not have
- been a representative sample.
- 5 (Screen.)
- Thirdly, there were issues in the dose-
- 7 response analysis, including that it was driven
- largely by a few outlier values and may therefore not
- 9 have been reliable.
- 10 It was also -- the study was also not
- 11 adjusted for location, and the investigators
- explained that the study was initially planned for
- the U.S. only, but was later expanded to the U.K.
- 14 after low enrollment.
- And in addition, there were no adjustments
- for multiplicity of analyses.
- 17 (Screen.)
- The NEAD investigators have assisted the FDA
- in a variety of ways and, in addition to sharing
- their data set, they also provided the division with
- an abstract of a study that assessed the data, the
- same NEAD data, this time at age four and a half, and

- they had similar findings to those at age three.
- They also shared an abstract of a recently
- 3 published study, again examining the effect of
- 4 breastfeeding during AED use on cognition, which
- 5 found no effect.
- The FDA also conducted a subsequent
- 7 literature search and found a handful of articles
- since the NEAD study that had looked at the issue,
- g and these replicated the lower cognitive score
- findings for valproate, although none were as large
- or comprehensive as the NEAD study.
- 12 (Screen.)
- Having assessed the totality of the data and
- examined the issues that were still pending at the
- prior advisory committee presentation, the DNP has
- reached a regulatory decision and has concluded that
- a description of the findings of the NEAD study
- pertaining to the risk for neurodevelopmental delays
- after in utero valproate exposure should be included
- in the label.
- This statement would be included in the
- 22 warnings-precautions section as well as in the

- pregnancy-related section of the labeling.
- 2 (Screen.)
- The division is currently finalizing this
  labeling, so we don't have the actual language to
  share with you at this time. However, the label will
  note that published epidemiologic studies have
  demonstrated that children exposed to valproate in
  utero have lower cognitive test scores than children
  exposed to either other AEDs or to no AEDs in utero.
- The largest of the studies, which is the 10 NEAD study, will be described and the labeling will 11 that, although all of the studies have 12 limitations, the methodological weight of the 13 evidence supports a causal association. 14
- So again, this presentation represented an update. So we actually do not have any questions for the committee.
- DR. MURPHY: But the committee can have questions for us.
- 20 CHAIRMAN ROSENTHAL: Are there questions? I
  21 would just like to start by thanking you just for
  22 following through on this and for circling back and

- $_{\mbox{\scriptsize 1}}$  closing the loop with the committee, and for your
- very strong work on behalf of children.
- 3 Dr. Holmes, did you have a comment or
- 4 question?
- DR. HOLMES: Could you show the last slide
- 6 again?
- 7 (Screen.)
- I just wondered, since Meador did not look
- g at a no-treatment group, how you came up with the
- 10 fact that valproate's worse than not being on anti-
- epileptic drugs.
- DR. JONES: That was based on the other
- studies beyond Dr. Meador's studies. We can go over
- the references, but there's other studies, including
- one prospective cohort study from Sweden that did
- 16 contain a null treatment group.
- DR. HOLMES: And you were pretty convinced
- 18 by those?
- DR. JONES: As mentioned, they were not as
- 20 high quality as the Meador study, but it was
- 21 additional data.
- DR. HOLMES: Because usually women that

- choose not to go on treatment often have a different
- type of epilepsy. There's a whole lot of different
- issues about those women, and whether their epilepsy
- is severe or not. I just have that concern, and just
- 5 be careful about the wording because not all the
- 6 drugs have been studied.
- 7 CHAIRMAN ROSENTHAL: Other comments or
- g questions?
- DR. SANTANA: I wonder if you're also going
- to address the issue -- I mean, you've looked at a
- lot of studies, but a big driver here is this NEAD
- study, and I just personally don't know where this is
- going, with everything that they've done in the
- 14 conduct of the study. They basically have been
- looking at their data so many times that when they
- reach their primary end point, which is this six-year
- 17 IQ, who's going to believe the data?
- So I think I'm not a biostatistician and I'm
- not a pathology expert, but I would wonder how
- 20 cautious we should be, even if that study turns out
- one way or the other, in terms of the conduct of the
- study, whether that data is ever going to be

- reasonable to justify what they want to do.
- DR. JONES: The division has certainly
- discussed those points. However, we've also
- d concluded that the NEAD study is likely the best data
- that we are likely to see certainly in any future
- 6 time period.
- 7 CHAIRMAN ROSENTHAL: Dr. Notterman.
- DR. NOTTERMAN: Have you reached a
- 9 reasonably firm conclusion that at this point there's
- no evidence of a class effect?
- DR. JONES: We have not fully explored that
- issue. The normed -- in the slides that presented
- the pre-IQ data, the norm is 100, and for the other,
- the non-valproate AEDs, they were generally, the mean
- scores were generally at the average score.
- DR. NOTTERMAN: Thanks.

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- CHAIRMAN ROSENTHAL: Yes, Dr. Holmes.
- DR. HOLMES: Just one last question for me.
- 20 How are you going to deal with this situation of
- women that are taking AEDs, but not for epilepsy?
- How will the labeling affect that group of people?

- People are taking it for migraine, for example.
- DR. JONES: As we mentioned, we are
- finalizing the labeling and we can consider that.
- Alice Hughes may have an additional comment.
- DR. HUGHES: This is Alice Hughes, the
- 6 Deputy Director for Safety in the Division of
- 7 Neurology Products. We already in the approved
- 8 labeling -- because of the risk of neural tube
- 9 defects, which is a longstanding concern for which we
- have very good data, the labeling already says that
- if valproate treatment is considered for illnesses
- that are not generally associated with death or that
- are not generally life-threatening, that serious
- 14 consideration be given to treatment with another
- anti-epileptic or no anti-epileptic.
- 16 It already says something very similar to
- that, and I think migraine is even used as a
- parenthetical example of such an illness. So it's
- good to keep in mind that this just adds to a very --
- 20 a label that has a lot of information about the
- 21 effects during pregnancy already, and this
- strengthens it even further.

1 CHAIRMAN ROSENTHAL: Dr. Towbin.

Well, just to comment along DR. TOWBIN: 2 those same lines. Actually, in psychiatry this drug 3 is used quite heavily outside of the indications for 4 bipolar disorder, and there is where I think you 5 might need to carefully consider how you're going to 6 word this. I think that its use for individuals who 7 have aggression, who have a variety of problems with 8 mood lability that don't reach a threshold for 9 bipolar disorder, and for other similar purposes, is 10 something that I don't think is appreciated as well. 11 That is, the risks here may not be balanced well. 12

There may be a way in which you could get data about the prevalence of those off-label uses, that also might help us in writing that language.

DR. HUGHES: Dr. Jones, we did look at some data about off-label use, but we looked at that a couple of years ago and there was a lot of psychiatric use.

DR. JONES: I was surprised by the amount of psychiatric use in women of childbearing age.

DR. TOWBIN: I am not.

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- 1 CHAIRMAN ROSENTHAL: All right, thank you.
- 2 Are there additional comments?
- 3 (No response.)
- 4 CHAIRMAN ROSENTHAL: Shall I?
- DR. MURPHY: I know I sound like a broken record, but thank you all. It has been a terrific meeting. I think we got some really good discussion, we got input, and that's what we need. I look
- forward to seeing many of you back here again.
- CHAIRMAN ROSENTHAL: Well, on behalf of the 10 committee, we appreciate all of the work that goes 11 into preparing for these meetings and all the work 12 that's done in each of the divisions to really turn 13 over all the rocks and explore all the issues and to 14 be so well prepared for these discussions. 15 appreciate that, and on behalf of the committee we 16 appreciate that. 17
- I would encourage people on the committee, if the agency calls you or sends you an email and asks if you can participate on one of the other advisory committees, I'd like you to try and do that if you can. You each have expertise that's needed in

1	some of the other forums and so in order to inform
2	those processes, the more we participate the better.
3	So thank you all very much. We appreciate
4	it. Great meeting, and safe travels home.
5	DR. MURPHY: Yes, safe travels, and we'll be
6	polling you some more for some more dates.
7	(Whereupon, at 5:45 p.m., the meeting was
8	adjourned.)
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